Table 3. HLA DNA typing of CBZ-induced ADR patients

No.	HLA low-resolution						HLA high-resolution	
	HLA-A		HLA-B		HLA-DR		HLA-B	
1	A26	A24	B62	B55	DR4	DR14	B*1507	B*5502
2	A2	A11	B75	B61	DR12	DR15	B*151101	B*400201
3	A31	A31	B56	B60	DR4	DR4	B*4001	B*5601
4	A24	A31	B60	B51	DR9	DR12	B*4001	B*510101
5	A31	A24	B51	B52	DR9	DR15	B*5101	B*5201
6	A2	A31	B46	B61	DR8	DR11	B*400201	B*4601
7	A2	A11	B51	B67	DR14	DR15	B*510101	B*670101
8	A11	A31	B7	B51	ND	ND	B*070201	B*510101
9	A31	A24	B61	B52	DR12	DR15	B*400201	B*520101
10	A24	A31	B54	B61	DR8	DR14	B*400201	B*5401
11	A31	A33	B44	B51	DR13	DR14	B*440301	B*510101
12	A24	A31	B51	B52	DR14	DR15	B*5101	B*5201
13	A24	A26	B13	B44	DR12	DR3	B*1310	B*440301
14	A11	A31	B51	B62	DR4	DR8	B*150101	B*510101
15	A11	A26	B55	B55	DR8	DR14	B*5502	B*5502

ADR, adverse drug reactions; CBZ, carbamazepine; HLA, human leukocyte antigen; ND, not done.

CBZ-induced ADR patients and the CBZ-tolerant patients, we found that the OR of A11, A31 and B51 were individually significantly high in the CBZ-induced ADR patients, as shown in Table 4. In particular, the OR of A31 was the highest ($P = 0.001$). Although the *P*-value of A11 was more than 0.05, we considered that the OR of A11 was significantly high because the 95% confidence interval (CI) of A11 did not range across 1.000. On the contrary, the OR of A2 was significantly low in the CBZ-induced ADR patients ($P = 0.04$). Table 5 shows the high-resolution HLA-B typing and their frequencies in the CBZ-induced ADR patients and CBZ-tolerant patients together with those reported for a general Japanese population.[32] The HLA-B*5101 genotype appeared significantly higher in the CBZ-induced ADR patients ($P = 0.031$). The OR of HLA-B*5101 was 4.900 and the 95% CI was 1.219–19.689. None of the 15 CBZ-induced ADR patients, including three SJS/TEN patients and 33 CBZ-tolerant patients, possessed the HLA-B*1502 genotype.

We also investigated the CBZ-induced proliferation of PBMC in each patient. The mean SI of CBZ-induced ADR patients ($382.1 \pm 295.1\%$, $n = 15$) was significantly high compared with that of CBZ-tolerant patients ($125.3 \pm 29.5\%$, $n = 32$, $P < 0.001$). Table 6 shows a comparison of DLST values, mean measurement day from onset and mean systemic steroid dose from onset to DLST measurement day between subjects with and without the HLA-A31 allele in CBZ-induced ADR patients. DLST values were also compared between subjects with and without the HLA-A31 allele in CBZ-tolerant patients. The mean SI was not significantly different between subjects with and without the HLA-A31 allele in both CBZ-induced ADR patients and CBZ-tolerant patients. The mean measurement day and the mean systemic steroid dose were not significantly different between subjects with and without the HLA-A31 allele in CBZ-induced ADR patients. No significant difference was seen in DLST values between subjects with or without the HLA-A11 allele or between subjects with or without A51 in CBZ-induced ADR patients and CBZ-tolerant patients (data not shown).

DISCUSSION

On the basis of previous reports of HLA associated with CBZ-induced ADR in a Japanese population,[7,15] we confirmed the association between HLA-A*3101 and CBZ-induced ADR, especially CBZ-induced DIHS. HLA-B*1502 was not found in either CBZ-induced ADR patients or CBZ-tolerant patients, compatible with previous results obtained from Japanese populations.[7,10,15,19,20] Altogether, HLA-B*1502 is strongly associated with SJS/TEN in Asians, but not in Japanese or Caucasians. On the other hand, HLA-A*3101 is well associated with SJS/TEN and DIHS in Japanese and Caucasians and, though to a somewhat lesser extent, associated with HSS/MPE in Asians.

The reason for the diversity of HLA association in CBZ-induced ADR among races is unclear. Similar diversity in HLA associated with rheumatoid arthritis (RA) has been observed. Since Isomäki *et al.*[33] first reported an association between RA and HL-A27 by mixed lymphocyte culture in 1974, associations between RA and HLA-DR4 have been reported in various races[34,35] but not in Spanish, Abrahamidae and Indian, in which an association with HLA-DR1 and DR10 was shown.[36,37] Compared with the amino acid sequence of HLA-DRB1 in HLA-DR4, -DR1 and -DR10, common amino acid sequences were found in positions 67–74 in the HLA-DRB1 molecule.[38] The common amino acid sequence is situated in the third super-variable area of the DRβ chain and constitutes a part of the α-helix,[38] which plays an integral role in antigen presentation. Thus, this common structure has been considered to be involved in the development of RA. Accordingly, we compared the amino acid sequences of HLA-A*3101, HLA-B*1502, and HLA-A*240201 which is one of the major Japanese HLA alleles. Table 7 shows the amino acid sequences of positions 61–80 in the α1-helix structure of HLA-B*1502, HLA-A*3101 and HLA-A*240201, whose areas have a huge variety of amino acid sequences, although other areas have relatively conserved amino acid sequences. Although six amino acid compositions are common between HLA-B*1502 and HLA-A*3101

Table 4. Statistical analysis in HLA typing of CBZ-induced ADR patients and CBZ-tolerant patients

HLA low-resolution	CBZ-induced ADR patients (n = 15)	CBZ-tolerant patients (n = 33)	OR	95% CI	P-value	HLA gene frequencies in Japanese (n = 371)
A1	0	2	0.103	0.004–2.418	1.000*	0.009
A2	3	17	0.235	0.056–0.991	0.040	0.222
A11	5	3	5.000	1.009–24.773	0.088*	0.083
A24	7	18	0.729	0.214–2.480	0.613	0.38
A26	3	8	0.781	0.175–3.483	1.000*	0.13
A30	0	1	0.699	0.027–18.157	1.000*	0.001
A31	10	5	11.200	2.668–47.105	0.001*	0.071
A33	1	4	0.518	0.053–5.074	1.000*	0.097
B7	1	4	0.518	0.053–5.074	1.000*	0.065
B13	1	2	1.107	0.093–13.248	1.000*	0.018
B27	0	1	0.699	0.027–18.157	1.000*	0.004
B35	0	7	0.114	0.006–2.136	0.082*	0.076
B37	0	1	0.699	0.027–18.157	1.000*	0.013
B39	0	1	0.699	0.027–18.157	1.000*	0.05
B44	2	1	4.923	0.410–59.112	0.227*	0.075
B46	1	3	0.714	0.068–7.493	1.000*	0.039
B48	0	2	0.103	0.004–2.418	1.000*	0.037
B51	7	5	4.900	1.129–19.689	0.031*	0.101
B52	3	8	0.781	0.175–3.483	1.000*	0.028
B54	1	5	0.400	0.043–3.760	0.650*	0.036
B55	2	2	2.385	0.303–18.788	0.579*	0.022
B56	1	1	2.286	0.133–39.203	0.532*	0.006
B58	0	2	0.103	0.004–2.418	1.000*	0.004
B59	0	1	0.699	0.027–18.157	1.000*	0.018
B60	2	4	1.115	0.181–6.878	1.000*	ND
B61	3	6	1.636	0.385–6.951	0.703*	ND
B62	2	4	1.115	0.181–6.878	1.000*	ND
B67	1	2	1.107	0.093–13.248	1.000*	0.003
B71	0	2	0.103	0.004–2.418	1.000*	ND
B75	1	1	2.286	0.056–0.991	0.532*	ND
DR1	0	5	0.168	1.009–24.773	0.167*	0.065
DR4	3	14	0.339	0.214–2.480	0.132	0.225
DR7	0	1	0.699	0.175–3.483	1.000*	0.003
DR8	4	6	1.636	0.027–18.157	0.703*	0.121
DR9	2	11	0.308	2.668–47.105	0.182*	0.012
DR11	1	2	1.107	0.107–15.598	1.000*	0.034
DR12	3	3	2.500	0.520–17.316	0.360*	0.051
DR13	2	4	1.115	0.211–8.249	1.000*	0.084
DR14	6	6	3.000	0.676–11.695	0.152*	0.09
DR15	5	12	0.875	0.291–4.109	0.839	0.185
DR16	0	2	0.103	0.021–10.386	1.000*	0.009

*Fisher's exact test, no mark; Pearson's χ^2-test. ADR, adverse drug reactions; CBZ, carbamazepine; CI, confidence interval; HLA, human leukocyte antigen; OR, odds ratio (determined using Haldone's modification, which adds 0.5 to all cells to accommodate possible zero counts); ND, no data.

(nos. 61, 64, 68, 72, 75 and 78), each amino acid sequence of HLA-A*240201 is also the same. These same amino acid compositions are commonly preserved in other HLA types and would not affect structural difference among the types. In addition, we found no common amino acid compositions of amino acids with polar characters (nos. 71, 80) or non-polar characters (nos. 62, 63, 65, 66, 67, 69, 70, 73, 74, 76, 77 and 79), which can affect 3-D conformation, between HLA-B*1502 and HLA-A*3101. Furthermore, no single amino acid was commonly present in alleles of both HLA-A*3101 and HLA-B*1502, except the amino acids present at the 61, 64, 68, 72, 75 and 78 positions. Therefore, HLA-B*1502 and HLA-A*3101 have no structural commonality for the common antigen presentation. We found no 3-D commonality between the two HLA from amino acid sequence, and significant difference in DLST values between subjects with and without the HLA-A31 allele in CBZ-induced ADR patients and CBZ-tolerant patients, which can mean severe ADR are independent of HLA structure and antigen presentation.

Another possibility for an association between the two HLA types and ADR is a linkage disequilibrium phenomenon in the HLA locus.

Table 5. Statistical analysis of HLA-B DNA typing of CBZ-induced ADR patients and CBZ-tolerant patients

HLA-B high-resolution	CBZ-induced ADR patients (n = 15)	CBZ-tolerant patients (n = 33)	OR	95% CI	P-value*	HLA gene frequencies in Japanese (n = 371)
07020	1	4	0.518	0.053–5.074	1.000	0.011
1301	0	1	0.699	0.027–18.157	1.000	0.065
1302	0	1	0.699	0.027–18.157	1.000	0.015
1310	1	0	6.931	0.266–180.436	0.313	0.003
1501	0	4	0.518	0.053–5.074	1.000	ND
1507	1	0	6.931	0.266–180.436	0.313	0.087
1511	1	1	2.286	0.133–39.203	0.532	0.007
1518	0	2	0.467	0.021–10.386	1.000	0.004
2704	0	1	0.699	0.027–18.157	1.000	0.015
3501	0	7	0.114	0.006–2.136	0.082	0.003
3701	0	1	0.699	0.027–18.157	1.000	0.076
3904	0	1	0.699	0.027–18.157	1.000	0.013
4001	2	4	1.115	0.181–6.878	1.000	0.001
4002	3	4	2.636	0.560–12.421	0.236	0.042
4006	0	2	0.103	0.004–2.418	1.000	0.086
4403	2	1	4.923	0.410–59.112	0.227	0.039
4601	1	3	0.714	0.068–7.493	1.000	0.087
4801	0	2	0.103	0.004–2.418	1.000	0.036
5101	6	5	4.900	1.219–19.689	0.031	0.030
5201	3	8	0.781	0.175–3.483	1.000	0.077
5401	0	5	0.400	0.043–3.760	0.650	0.107
5502	2	2	2.385	0.303–18.788	0.579	0.077
5601	1	1	2.286	0.133–39.203	0.532	0.019
5801	0	2	0.103	0.004–2.418	1.000	0.005
5901	0	1	0.699	0.027–18.157	1.000	0.004
6701	1	2	1.107	0.093–13.248	1.000	0.018

*Fisher's exact test. ADR, adverse drug reactions; CBZ, carbamazepine; CI, confidence interval; HLA, human leukocyte antigen; OR, odds ratio (determined using Haldone's modification, which adds 0.5 to all cells to accommodate possible zero counts); ND, no data.

Table 6. Comparison of DLST between subjects with or without HLA-A31 allele in CBZ-induced ADR patients and CBZ-tolerant patients

Subjects	HLA-A31	n	DLST (c.p.m.)	P-value	Measurement (day)*	P-value	Total systemic steroid (mg)†	P-value
CBZ-induced ADR patients	(+)	10	302.8 ± 140.5	0.147	72 ± 70	0.111	3128 ± 2440	0.212
	(−)	5	540.6 ± 461.7		25 ± 16		1827 ± 3577	
CBZ-tolerant patients	(+)	4	103.3 ± 27.8	0.167				
	(−)	28	128.5 ± 28.8					

*Measurement day from onset. †Hydrocortisone titer conversion administrated until DLST measurement day. ADR, adverse drug reactions; CBZ, carbamazepine; c.p.m., counts per minute; DLST, drug-induced lymphocyte stimulation test; HLA, human leukocyte antigen.

Table 7. Amino acid sequence of α1-helix structure in human leukocyte antigen

Allele	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
B*1502	D	R	N	T	Q	I	S	K	T	N	T	Q	T	Y	R	E	S	L	R	N
A*3101	D	Q	E	T	R	N	V	K	A	H	S	Q	I	D	R	V	D	L	G	T
A*240201	D	E	E	T	G	K	V	K	A	H	S	Q	T	D	R	E	N	L	R	I

Near the HLA gene, several inflammatory cytokine genes are mapped, such as g-interferon and tumor necrosis factor-β.[39] The genes located in these areas are highly polymorphic, some involving single-nucleotide polymorphism. If a disease-sensitivity gene exists in close association with a HLA gene, the disease seems to be caused by the HLA type. An association between HLA-B51 and Behcet's disease is such an example.[40] Thus, a pathogenic gene for CBZ-induced ADR might be strongly connected to HLA-B*1502 in Han Chinese and Asians, but the gene might be connected to HLA-A*3101 in Europeans and Japanese. However, a recent

detailed genome-wide association study concerning CBZ-induced ADR indicated that the CBZ-induced ADR gene is located at the HLA locus area; thus, it is not likely that another gene with polymorphisms causes CBZ-induced ADR.

A second possible reason is that HLA-B*1502 is associated with SJS/TEN, but not with HSS/DIHS or MPS, whereas HLA-A*3101 is associated with HSS/DIHS, but not with SJS/TEN. HLA-B*1502 was found to be specific to CBZ-induced SJS/TEN, and no association was seen in patients with CBZ-induced HSS or MPE in Han Chinese residing in Taiwan.[2] In addition, no association with HLA-B*1502 was confirmed in Caucasian patients with HSS.[16] Recently, an association between HLA-A*3101 and CBZ-induced ADR was reported in both the Japanese and Europeans by genome-wide approaches.[15,16] In the present study, we found an association between HLA-A31 and DIHS, but only one of three patients with SJS/TEN had HLA-A31, supporting this hypothesis.

Human leukocyte antigen is well documented to be associated with some chronic inflammatory diseases and autoimmune diseases; for instance, HLA-B27 is strongly associated with Reiter syndrome and ankylosing spondylitis. Thereby, the HLA molecule plays some role in the pathogenesis by modulating the immune system. In the present study, we also tested the association between HLA-A31 and SI of DLST. We failed to demonstrate the HLA-A31-associated enhancement of lymphocyte proliferation (Table 6), although we were able to confirm strong lymphocyte activation with CBZ in the patient group.

We found that HLA-A11 and HLA-A51 are weakly associated with CBZ-induced ADR patients. Because the number of cases was small in the present study, we cannot confirm the presence of an association. We need to evaluate more cases to ascertain an association between other HLA alleles and CBZ-induced ADR patients.

In the present study, we confirmed a strong association between HLA-A31 and CBZ-induced ADR in a Japanese population. However, HLA-A31 does not determine CBZ-induced lymphocyte proliferation.

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LETTER TO THE EDITOR

Case of carbamazepine-induced hypersensitivity syndrome associated with human leukocyte antigen-A*3101

Dear Editor,

In 2008, Mallal *et al.*[1] reported that a hypersensitivity reaction to abacavir, a reverse transcriptase inhibitor of HIV, was strongly associated with human leukocyte antigen (HLA)-B*5701. In addition, it was indicated that HLA-B*5701 screening can reduce the risk of a hypersensitivity reaction to abacavir and a pharmacogenetic test was found to be useful for preventing a specific toxic effect of the drug.[1] Furthermore, carbamazepine (CBZ)-induced cutaneous adverse drug reactions (cADR), including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS), have been shown to be closely associated with HLA.[2,3] Ozeki *et al.*[4] demonstrated that HLA-A*3101 is significantly associated with susceptibility to DIHS induced by CBZ in the Japanese population. It remains unclear how DIHS develops but these reports shed light on the pathogenesis of DIHS and are expected to promote the development of a genetic test for identifying individuals at risk for this potentially life-threatening condition caused by CBZ.

The patient was a 62-year-old female. One month after CBZ for trigeminal neuralgia, she became ill with fever, a sore throat and an erythematous maculopapular eruption. Three weeks after becoming ill, the patient was admitted to our hospital. At that time her temperature was 38.6°C and she had gained 5 kg of bodyweight. Her neck lymph nodes were enlarged and erythroderma was evident. Leukocytosis, eosinophilia and liver dysfunction were present. A comparison of virus antibody values on the 1st day (human herpesvirus [HHV]-6 immunoglobulin [Ig]G, 10; cytomegalovirus [CMV] IgG, 13.3) and the 30th day (HHV-6 IgG, 80; CMV IgG, >128), indicated revitalization of HHV-6 and CMV. The drug lymphocyte stimulating test (DLST) of CBZ was positive (SI = 281%). The diagnosis was DIHS-induced CBZ on the basis of physical examination, blood tests, medication with CBZ and a positive reaction to DLST. First, we suspended treatment with CBZ and administrated 60 mg/day of prednisolone by drip infusion for 3 days. We then administrated 40 mg/day of prednisolone tablets for 7 days with subsequent tapering. Four weeks after admission, all symptoms disappeared, and 114 days after admission, the prednisolone course was complete. Eighty-three days after completion of the course of prednisolone, the patient acquired indolent thyroiditis (Table 1, Fig. 1). After providing consent, high-resolution HLA serum typing of this case was performed by using a reverse sequence-specific oligonucleotide polymerase chain reaction (PCR-rSSO) method (Mitsubishi-Chemical BCL Laboratory, Tokyo, Japan). The HLA-A*3101 allele was confirmed to be present.

Carbamazepine is a frequently used anticonvulsant agent, which occasionally induces drug eruption. It is one of a few drugs that produce various cADR such as DIHS. The pathogenesis of the drug reaction is unclear because pathological analysis still has not been established due to the diverse forms of reactions, factors and modifiers and the absence of a suitable animal model. Therefore, even though drug eruption is a common disorder, it tends to get short shrift and potentially life-threatening conditions such as DIHS are not well recognized.

Table 1. Examinations of thyroid function

F-T3 4.38 (2.1–4.1 pg/mL)
F-T4 1.80 (1.0–1.7 pg/mL)
Thyroid-stimulating hormone 0.05 (0.436–3.78 μU/mL)
Anti-thyroid antigen (–)

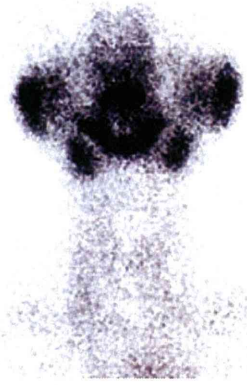

Figure 1. No uptake of technetium-99*m* was identified in the thyroid. F-T3 and FT-4 were high and thyroid-stimulating hormone was suppressed. Furthermore, anti-thyroid antigen did not appear. We then made a diagnosis of indolent thyroiditis.

In 2011, Ozeki *et al.* found that 12 single nucleotide polymorphisms significantly associated with CBZ-induced cADR are located within a 463-kb region on chromosome 6p (21,33). It is notable that this region corresponds to the major histocompatibility complex (MHC) class I region containing the HLA-A locus.[4] The individual HLA-A alleles were genotyped for 61 cases that developed cADR and 376 cases that did not develop cADR with administration of CBZ. It was found that the HLA-A*3101 allele was present in 60.7% (37/61) of the cases with CBZ-induced cADR, but in only 12.5% (47/376) of the CBZ-tolerant controls (odds ratio = 10.8). This implies that the allele has 60.7% sensitivity and 87.5% specificity when applied as a risk predictor for CBZ-induced cADR.[4] This report suggested that for certain drugs, HLA alleles which code

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MHC class I molecules are significantly associated with cADR with respect to pathogenesis.

In therapy for HIV infection, pharmacogenetic tests are useful for preventing specific toxic effects of drugs.[1] If pharmacogenomics tests had been administered for our case in the same manner before onset of disease, other anti-neuralgia agents may have been chosen and the complications would have been avoided. It would be ideal if profiling analysis of HLA alleles could be performed in certain geographical areas on a mass scale and if clinical applications of gene analysis could be generalized from this point forward.

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SPECIAL REPORT

Prevalence of dermatological disorders in Japan: A nationwide, cross-sectional, seasonal, multicenter, hospital-based study

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ABSTRACT

To clarify the prevalence of skin disorders among dermatology patients in Japan, a nationwide, cross-sectional, seasonal, multicenter study was conducted in 69 university hospitals, 45 district-based pivotal hospitals, and 56 private clinics (170 clinics in total). In each clinic, information was collected on the diagnosis, age, and gender of all outpatients and inpatients who visited the clinic on any one day of the second week in each of May, August, and November 2007 and February 2008. Among 67 448 cases, the top twenty skin disorders were, in descending order of incidence, miscellaneous eczema, atopic dermatitis, tinea pedis, urticaria/angioedema, tinea unguium, viral warts, psoriasis, contact dermatitis, acne, seborrheic dermatitis, hand eczema, miscellaneous benign skin tumors, alopecia areata, herpes zoster/postherpetic neuralgia, skin ulcers (nondiabetic), prurigo, epidermal cysts, vitiligo vulgaris, seborrheic keratosis, and drug eruption/toxicoderma. Atopic dermatitis, impetigo, molluscum, warts, acne, and miscellaneous eczema shared their top-ranking position in the pediatric population, whereas the most common disorders among the geriatric population were tinea pedis, tinea unguium, psoriasis, seborrheic dermatitis, and miscellaneous eczema. For some disorders, such as atopic dermatitis, contact dermatitis, urticaria/angioedema, prurigo, insect bites, and tinea pedis, the number of patients correlated with the average high and low monthly temperatures. Males showed a greater susceptibility to some diseases (psoriasis, erythroderma, diabetic dermatoses, *inter alia*), whereas females were more susceptible to others (erythema nodosum, collagen diseases, livedo reticularis/racemosa, hand eczema, *inter alia*). In conclusion, this hospital-based study highlights the present situation regarding dermatological patients in the early 21st century in Japan.

Key words: age, Japan, prevalence, sex, skin diseases.

INTRODUCTION

Skin forms the outermost part of the human body and it acts as a vital barrier to external and internal damage. Various external and internal stimuli, which can be either short- or long-term, can affect the homeostasis of the skin, leading to a variety of disorders. The development and perpetuation of skin disorders are multifactorial in nature, and can result from genetic, environmental, mechanical, meteorological and even cultural effects. Skin disorders therefore include a vast range of diseases.

Although it is difficult to know the exact prevalence or incidence of skin diseases, several hospital-based

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studies have shown that skin diseases are very common. Of a total of 11 191 patients seen by a general practitioner in the UK, 2386 (21%) presented dermatological complaints. Among these there was a preponderance of females (1604, 67%), and the most common skin diseases seen were viral warts, eczema and benign tumors.[1] In the Netherlands, 235–460/1000 person-years of children aged 0–17 years contacted general practitioners in 1987 and 2001,[2] and these contacts frequently involved bacterial, viral, fungal, eczematous or traumatic skin diseases.[2] Tamer *et al.* reported on 6300 pediatric cases aged 0–16 years who visited dermatological clinics in Turkey; this group showed a preponderance of bacterial, viral and eczematous skin diseases.[3] In the case of Japan, there is no authentic report in the published work on any investigation of the prevalence of skin diseases; therefore, the Japanese Dermatological Association conducted a nationwide, cross-sectional, seasonal, multicenter, hospital-based study.

METHODS

A total of 190 dermatology clinics at 76 university hospitals, 55 district-based pivotal hospitals and 59 private clinics participated in this study. At each clinic,

Table 1. Numbers of patients recruited in each season

	Number of patients				
	May 2007	August 2007	November 2007	February 2008	Total
University Hospitals $n = 69$	8558	7944	7782	7778	32 062 (47.54%)
District-based Hospitals $n = 45$	3505	3450	2890	2864	12 709 (18.84%)
Private clinics $n = 56$	5779	6709	5364	4825	22 677 (33.62%)
Total	17 842	18 103	16 036	15 467	67 448 (100%)

Table 2. Age distribution and sex difference of patients

Age distribution (years old)	Number of patients	Male patients	Female patients	Sex undescribed
0–5	4192 (6.22%)	2200 (7.12%)	1983 (5.49%)	9
6–10	2099 (3.11%)	1047 (3.39%)	1047 (2.9%)	5
11–15	1711 (2.54%)	815 (2.64%)	893 (2.47%)	3
16–20	2270 (3.37%)	995 (3.22%)	1266 (3.5%)	9
21–25	3219 (4.77%)	1245 (4.03%)	1960 (5.43%)	14
26–30	3516 (5.21%)	1378 (4.46%)	2126 (5.89%)	12
31–35	4050 (6%)	1546 (5%)	2483 (6.87%)	21
36–40	3807 (5.64%)	1604 (5.19%)	2180 (6.03%)	23
41–45	3298 (4.89%)	1387 (4.49%)	1879 (5.2%)	32
46–50	3201 (4.75%)	1326 (4.29%)	1848 (5.12%)	27
51–55	4062 (6.02%)	1763 (5.71%)	2279 (6.31%)	20
56–60	5543 (8.22%)	2503 (8.1%)	3012 (8.34%)	28
61–65	5413 (8.03%)	2533 (8.2%)	2846 (7.88%)	34
66–70	5629 (8.35%)	2775 (8.98%)	2824 (7.82%)	30
71–75	6157 (9.13%)	3195 (10.34%)	2923 (8.09%)	39
76–80	4777 (7.08%)	2487 (8.05%)	2259 (6.25%)	31
81–85	2636 (3.91%)	1297 (4.2%)	1318 (3.65%)	21
86–90	1098 (1.63%)	508 (1.64%)	583 (1.61%)	7
91–100	427 (0.63%)	166 (0.54%)	259 (0.72%)	2
≥101	16 (0.02%)	3 (0.01%)	2 (0.01%)	11
Age undescribed	327 (0.48%)	126 (0.41%)	155 (0.43%)	46
Total	67 448 (100%)	30 899 (100%)	36 125 (100%)	424

information on diagnosis, age and sex was collected from all outpatients and inpatients who visited the clinics or who were hospitalized on any single day of the second week in each of May, August and November 2007 and February 2008. Reports on the monthly average values of the high and low temperatures and humidities were collected from the Meteorological Agency. The information on 67 448 cases from 170 clinics (69 university hospitals, 45 district-based pivotal hospitals and 56 private clinics) that participated in all of the four seasonal examinations was analyzed. Statistical analyses were performed by using Spearman's rank correlation coefficient. A *P*-value of <0.05 was considered to be statistically significant. This study was approved by the internal ethical review boards of the Japanese Dermatological Association.

Table 3. Prevalence of skin diseases in 67 448 patients

Burn	899 (1.33%)	Syphilis	24 (0.04%)
Trauma	409 (0.61%)	Miscellaneous sexually transmitted diseases	41 (0.06%)
Skin ulcer (nondiabetic)	1334 (1.98%)		
Pressure ulcer	608 (0.9%)	Bullous pemphigoid	510 (0.76%)
Miscellaneous physico-chemical skin damage	681 (1.01%)	Pemphigus	424 (0.63%)
		Miscellaneous bullous diseases	141 (0.21%)
Diabetic dermatoses	436 (0.65%)	Systemic sclerosis	619 (0.92%)
Atopic dermatitis	6733 (9.98%)	Systemic lupus erythematosus	525 (0.78%)
Hand eczema	2024 (3%)	Dermatomyositis	304 (0.45%)
Contact dermatitis	2643 (3.92%)	Miscellaneous collagen diseases	915 (1.36%)
Seborrheic dermatitis	2213 (3.28%)	Anaphylactoid purpura	171 (0.25%)
Miscellaneous eczema	12590 (18.67%)	Reticular/racemous livedo	81 (0.12%)
Urticaria/angioedema	3369 (4.99%)	Miscellaneous vasculitis/purpura/ circulatory disturbance	632 (0.94%)
Prurigo	1229 (1.82%)		
Drug eruption/toxicoderma	1018 (1.51%)	Mycosis fungoides	427 (0.63%)
Psoriasis	2985 (4.43%)	Miscellaneous lymphomas	285 (0.42%)
Palmoplantar pustulosis	832 (1.23%)	Pigmented nevus	709 (1.05%)
Miscellaneous pustulosis	172 (0.26%)	Seborrheic keratosis	1095 (1.62%)
Lichen planus	200 (0.3%)	Soft fibroma/acrochordon	231 (0.34%)
Miscellaneous inflammatory keratotic disorders	241 (0.36%)	Epidermal cyst	1194 (1.77%)
		Lipoma	173 (0.26%)
Tylosis/clavus	917 (1.36%)	Dermatofibroma	111 (0.16%)
Ichthyosis	61 (0.09%)	Miscellaneous benign skin tumors	1666 (2.47%)
Miscellaneous keratinization disorders	502 (0.74%)	Actinic keratosis	261 (0.39%)
Ingrown nail	597 (0.89%)	Basal cell carcinoma	324 (0.48%)
Miscellaneous nail disorder	397 (0.59%)	Squamous cell carcinoma/Bowen's disease	455 (0.67%)
Alopecia areata	1653 (2.45%)		
Androgenic alopecia	210 (0.31%)	Paget's disease	224 (0.33%)
Miscellaneous skin appendage disorders	266 (0.39%)	Malignant melanoma	808 (1.2%)
Scabies	98 (0.15%)	Miscellaneous malignant skin tumors	534 (0.79%)
Insect bite	762 (1.13%)	Vitiligo vulgaris	1134 (1.68%)
Tinea pedis	4379 (6.49%)	Chloasma/senile freckle	336 (0.5%)
Tinea unguium	3231 (4.79%)	Miscellaneous pigmented disorders	154 (0.23%)
Miscellaneous tinea	610 (0.9%)	Erythema multiforme	197 (0.29%)
Candidiasis	408 (0.6%)	Erythema nodosum	111 (0.16%)
Miscellaneous mycosis	211 (0.31%)	Miscellaneous disorders with erythematous plaques	130 (0.19%)
Acne	2430 (3.6%)		
Impetigo contagiosum	507 (0.75%)	Nevus/phacomatosis (other than pigmented nevus)	267 (0.4%)
Folliculitis	755 (1.12%)		
Erysipelas	81 (0.12%)	Rosacea/rosacea-like dermatitis	150 (0.22%)
Cellulitis	594 (0.88%)	Granulomatous diseases	192 (0.28%)
Miscellaneous bacterial infection	914 (1.36%)	Keloid/hypertrophic scar	186 (0.28%)
Molluscum contagiosum	604 (0.9%)	Cheilitis/angular cheilitis/mucous membrane diseases	95 (0.14%)
Herpes simplex	691 (1.02%)		
Herpes zoster/zoster-associated pain	1609 (2.39%)	Erythroderma	63 (0.09%)
Viral wart	3028 (4.49%)	Other diseases	666 (0.99%)
Miscellaneous viral disorders	353 (0.52%)	Total	67 448 (100%)

RESULTS

Demographic data for the 67 448 patients

Among the 67 448 patients, 32 062 (47.54%) cases were recruited from university hospitals, 12 709 (18.84%) from district-based hospital and 22 677 (33.62%) from private clinics (Table 1). More patients were enrolled in August 2007 (18 103) than in February 2008 (15 467) (Table 1). With regards to the age distribution, the group aged 71–75 years (6157; 9.13%) was the biggest, followed by groups aged 66–70 (5629; 8.35%), 56–60 (5543; 8.22%) and 61–65 (5413; 8.03%) (Table 2). For patients aged under 20 years, the group aged 0–5 years formed the biggest population (4192; 6.22%). Among the 67 448 patients, there were 30 899 (46.1%) males and 36 125 (53.9%) females; the sex of 424 patients was not described. Female patients aged between 16 and 60 years tended to visit dermatology clinics more frequently than their male counterparts (Table 2).

Prevalence of skin disorders

We classified skin diseases into 85 categories, as listed in Table 3, and determined the prevalence of each. The 20 most common diseases were miscellaneous eczema (12 590; 18.67%) followed, in order, by atopic dermatitis (6733; 9.98%), tinea pedis (4379; 6.49%), urticaria/angioedema (3369; 4.99%), tinea unguium (3231; 4.79%), viral warts (3028; 4.49%), psoriasis (2985; 4.43%), contact dermatitis (2643, 3.92%), acne (2430; 3.6%), seborrheic dermatitis (2213; 3.28%), hand eczema (2024; 3%), miscellaneous benign skin tumors (1666; 2.47%), alopecia areata (1653; 2.45%), herpes zoster/zoster-associated

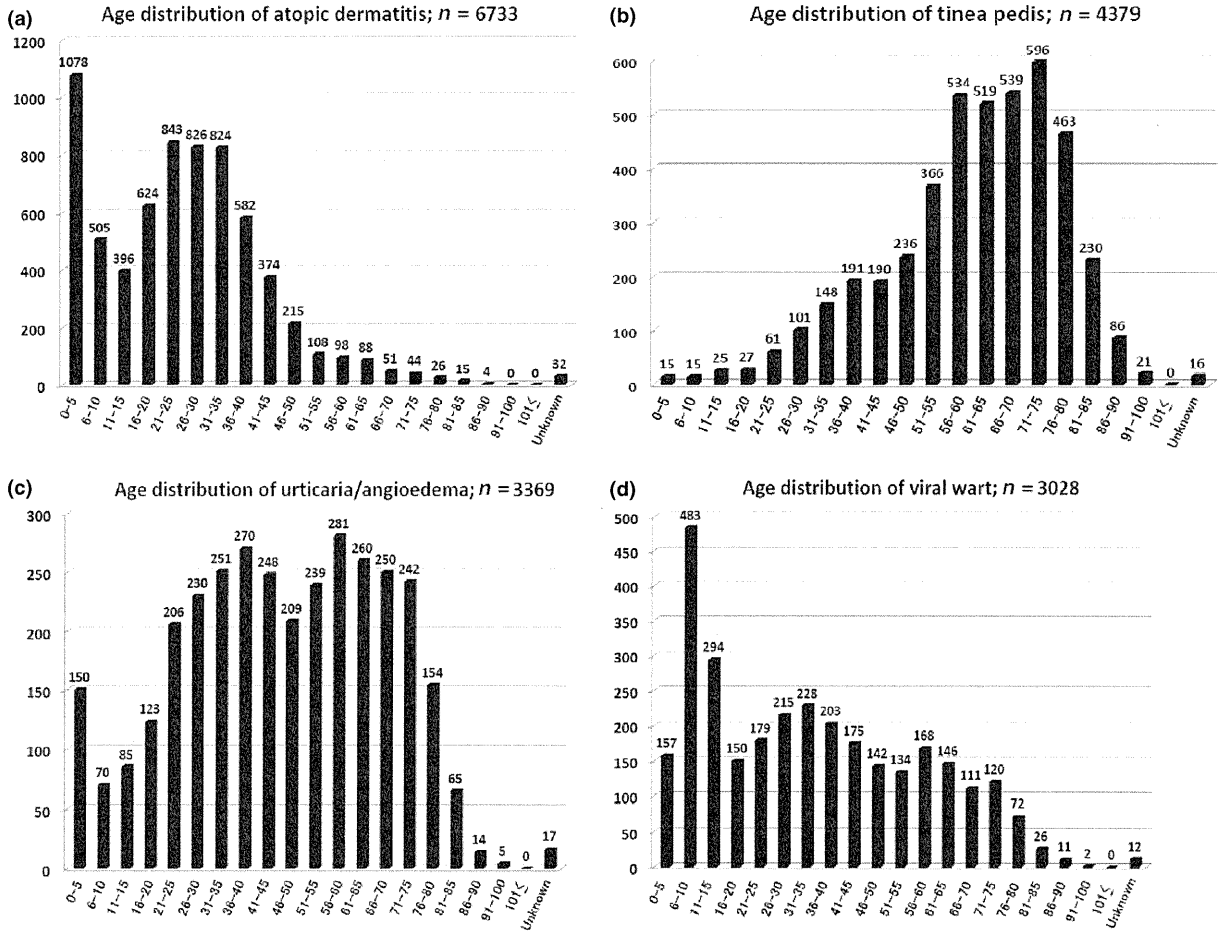

Figure 1. Age distribution of atopic dermatitis, tinea pedis, urticaria/angioedema and viral wart.

pain (1609; 2.39%), skin ulcers (non-diabetic) (1334; 1.98%), prurigo (1229; 1.82%), epidermal cysts (1194; 1.77%), vitiligo vulgaris (1134; 1.68%), seborrheic keratosis (1095; 1.62%) and drug eruption/toxicoderma (1018; 1.51%). These top 20 categories covered 57 577 (85.34%) of the 67 448 patients (Table 3).

Age distributions of common diseases

The age distribution of atopic dermatitis was biphasic, peaking at 0–5 and 21–35 years of age (Fig. 1a). Tinea pedis peaked at 56–75 years of age (Fig. 1b). Tinea unguium showed a similar pattern (data not shown). Urticaria/angioedema showed a triphasic distribution pattern (Fig. 1c), whereas viral warts peaked at 6–15 years of age (Fig. 1d). Psoriasis peaked at 56–65 years of age (Fig. 2a). The age distribution for contact dermatitis was somewhat evenly dispersed (Fig. 2b). The peak age for acne was 16–25 years (Fig. 2c), whereas that for seborrheic dermatitis was 71–75 (Fig. 2d). Hand eczema was distributed evenly in adults (Fig. 3a). The peak age for alopecia areata was 31–35 years (Fig. 3b). Herpes zoster/zoster-associated pain and prurigo were prominent in elderly patients (Fig. 3c,d). Epidermal cysts occurred in adults of all ages (Fig. 4a). Vitiligo vulgaris and drug eruption/toxicoderma were preponderant in elderly people (Fig. 4b,c). Notably, the age distribution for burns peaked in the group aged 0–5 years (Fig. 4d).

In Tables 4 and 5, we list the top five skin disorders for each age group. Miscellaneous eczema appeared in every age group, whereas atopic dermatitis was among the top five diseases for age groups under 50 years. The disease encountered most frequently in groups aged 6–40 years was atopic dermatitis.

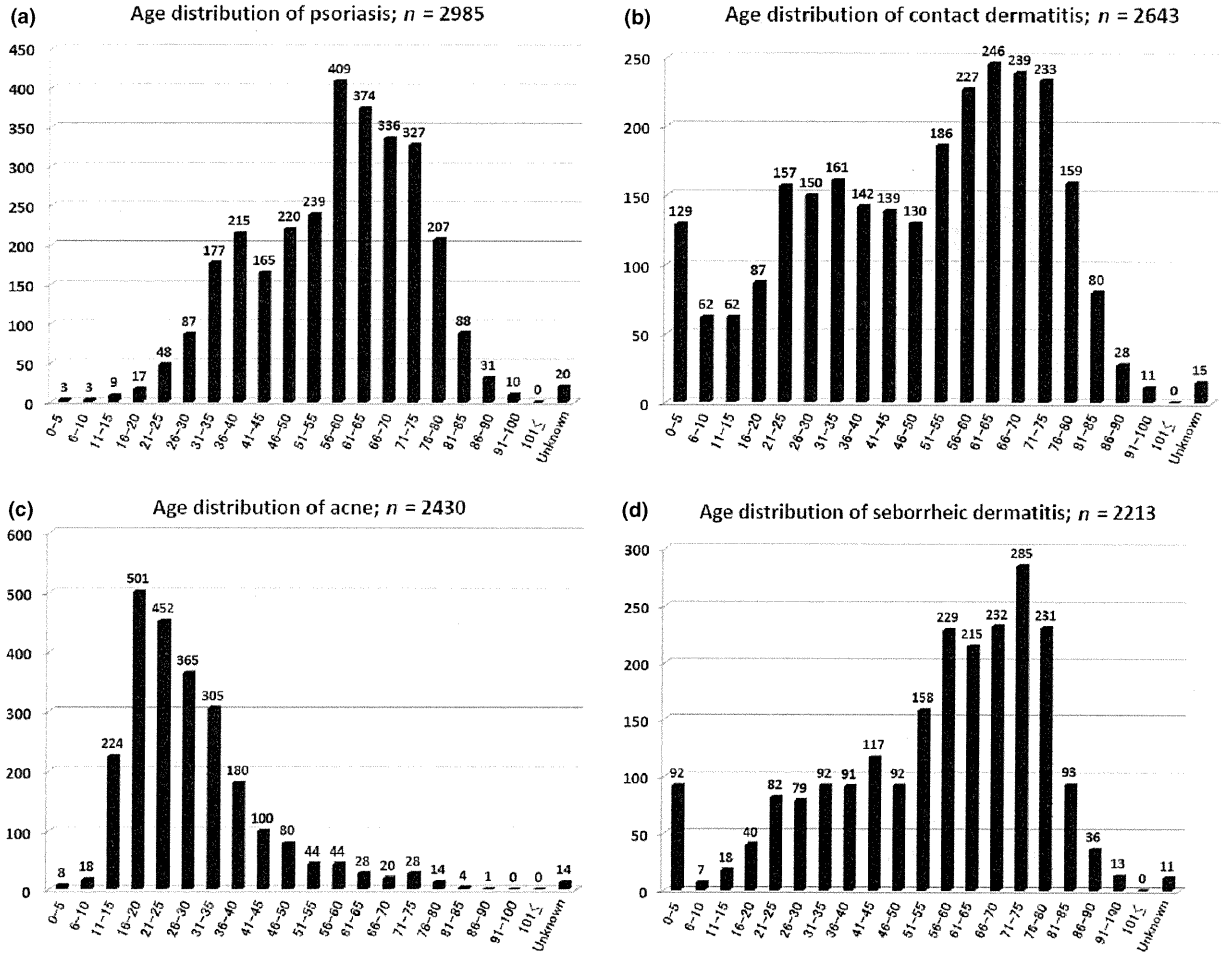

Figure 2. Age distribution of psoriasis, contact dermatitis, acne and seborrheic dermatitis.

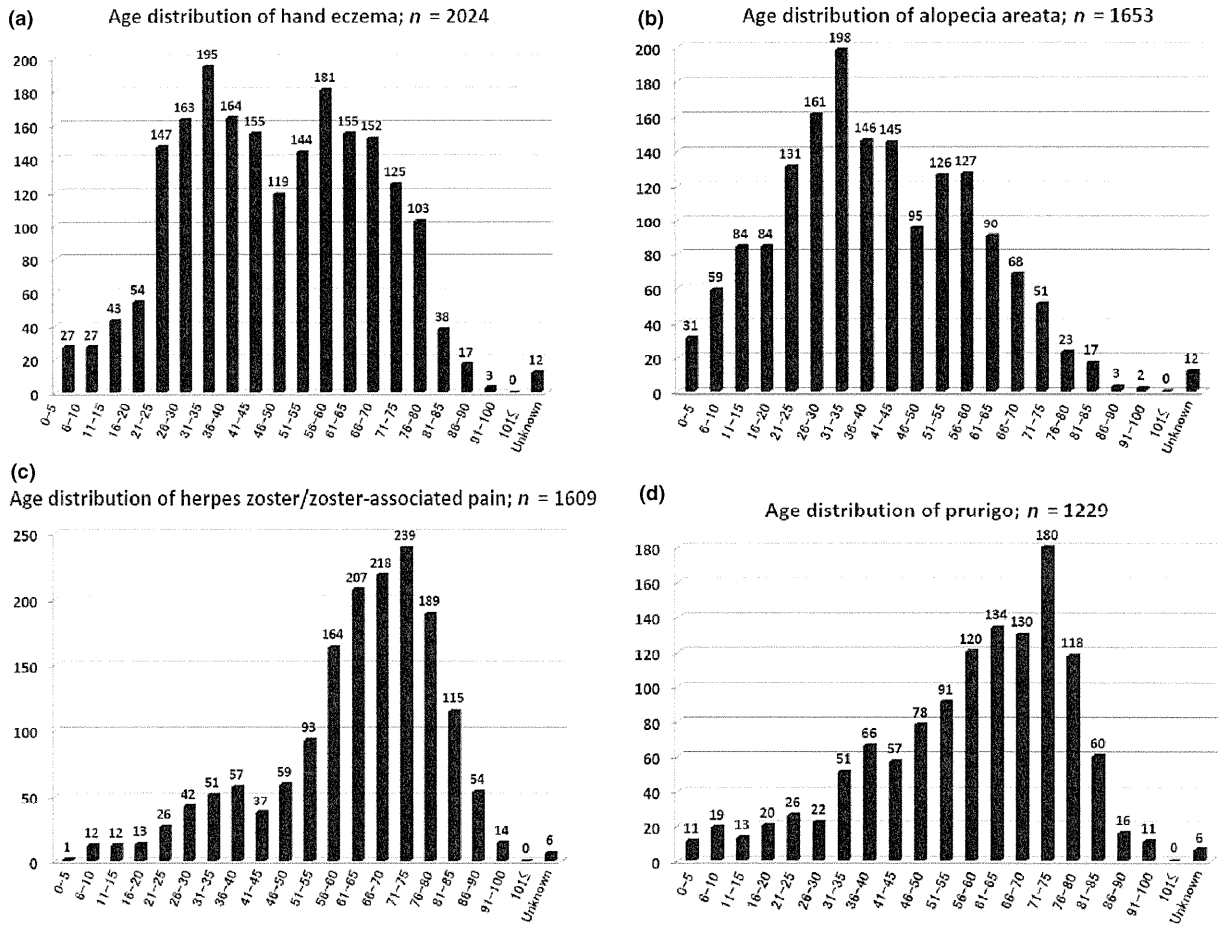

Figure 3. Age distribution of hand eczema, alopecia areata, herpes zoster/zoster-associated pain and prurigo.

Molluscum and impetigo were common in patients aged 0–10 years. Viral warts were among the top five diseases for groups aged 6–45 years. Acne was common in groups aged 11–35 years. Urticaria/angioedema was among the top five diseases for a wide range of age groups from 11–70 years old. Tinea pedis was common in groups aged above 41 years old. Psoriasis appeared in the top five diseases in middle-aged and older people with ages ranging 46–80 years old.

Sex differences

Difference in the incidence of skin disorders between the sexes are shown in Table 6. The prevalence of diabetic dermatoses, psoriasis, androgenic alopecia, syphilis and erythroderma in males was more than twice that in females, whereas the prevalence of hand eczema, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, reticular/racemous livedo, pigmented nevus, chloasma/senile freckle, erythema nodosum and rosacea/rosacea-like dermatitis was more than twice as high in females than males (Table 6).

Correlation between patient numbers and the average low temperature, average high temperature and average humidity in the months of clinic visits

Because this study was a nationwide survey for Japan, a wide variation of climates had to be considered. We therefore searched for correlations between patient numbers and average low temperature, average high temperature and average humidity of the month in which patients visited clinics. The numbers of visiting patients diagnosed with urticaria/angioedema (Fig. 5), insect bites (Fig. 5), tinea pedis (Fig. 6)

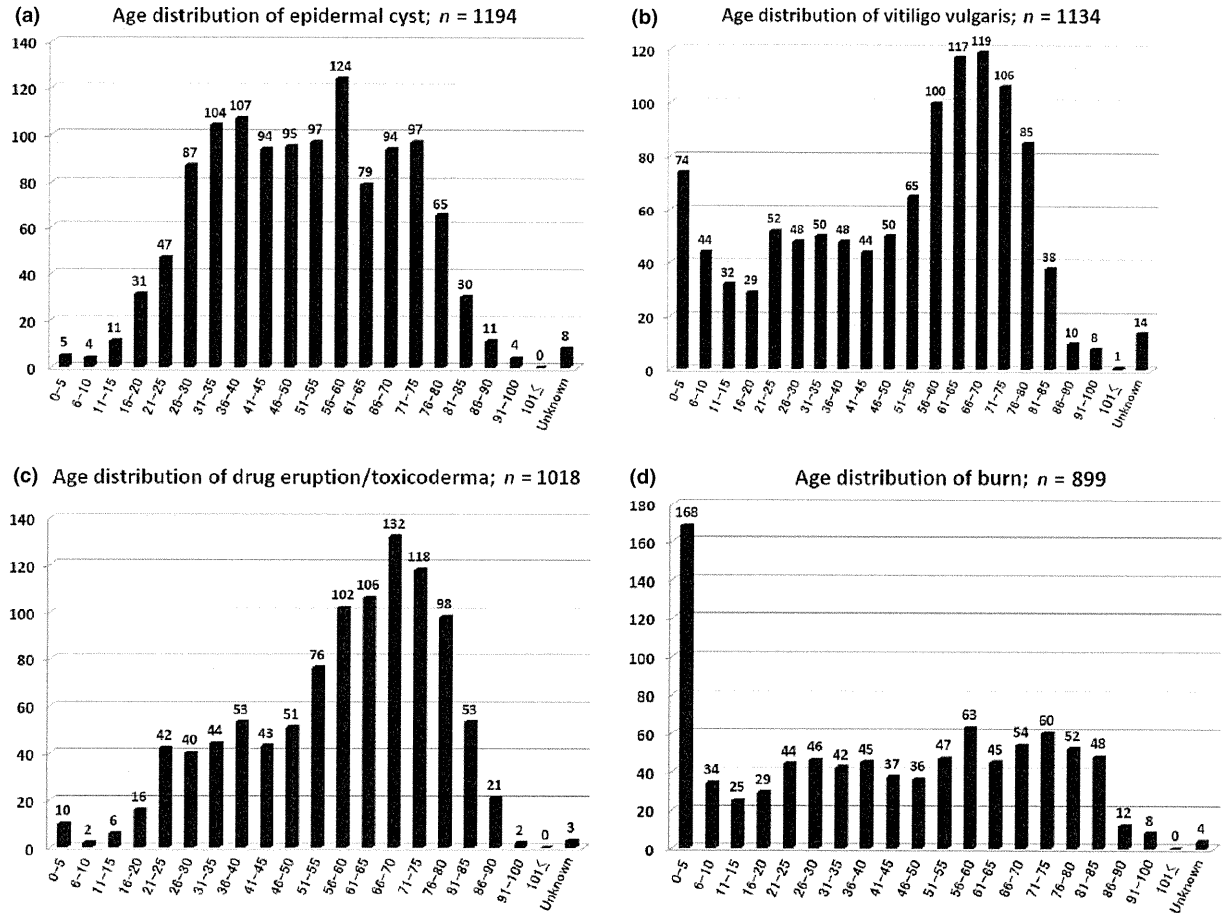

Figure 4. Age distribution of epidermal cyst, vitiligo vulgaris, drug eruption/toxicoderma and burn.

or impetigo (Fig. 6) showed a significant correlation with the average low temperature and with the average high temperature (data not shown). The numbers of visiting patients diagnosed with atopic dermatitis, contact dermatitis or molluscum contagiosum were also positively correlated with the average low temperature and average high temperature (data not shown). The numbers of patients diagnosed with seborrheic dermatitis showed a negative correlation with the average humidity (Fig. 7). The average humidity was also significantly and negatively correlated with atopic dermatitis, hand eczema and prurigo (data not shown).

DISCUSSION

There are a number of limitations and biases in hospital-based prevalence studies, including institutional specificity (university hospital, pivotal local hospital or private clinic), differences in localization, climatic and seasonal differences, and differences in skills in diagnosis.[1,4–6] This study, conducted in fiscal year 2007 by the Japanese Dermatological Association, recruited 76 university hospitals, 55 district-based pivotal hospitals and 59 private clinics (190 clinics in total). We analyzed data for 67 448 patients that were collected seasonally from 170 clinics. This nationwide study is first of its kind in Japan, and its nature appears to eliminate, at least in part, some of the above-mentioned biases of hospital-based prevalence study.

In fiscal year 2007, eczematous and fungal diseases were commonly reported in dermatological clinics in Japan. The 20 most common categories of skin disorder were diagnosed in more than 85% of patients presenting dermatological complaints. A

Table 4. Top five skin disorders in each age group

0–5 years old (*n* = 4192)	
Miscellaneous eczema	1229; 29.32%
Atopic dermatitis	1078; 25.72%
Molluscum contagiosum	425; 10.14%
Impetigo contagiosum	291; 6.94%
Miscellaneous benign skin tumors	226; 5.39%
6–10 years old (*n* = 2099)	
Atopic dermatits	505; 24.06%
Viral wart	483; 23.01%
Miscellaneous eczema	355; 16.91%
Molluscum contagiosum	144; 6.86%
Impetigo contagiosum	110; 5.24%
11–15 years old (*n* = 1711)	
Atopic dermatits	396; 23.14%
Viral wart	294; 17.18%
Acne	224; 13.09%
Miscellaneous eczema	214; 12.51%
Urticaria/angioedema	85; 4.97%
16–20 years old (*n* = 2270)	
Atopic dermatits	624; 27.49%
Acne	501; 22.07%
Miscellaneous eczema	269; 11.85%
Viral wart	150; 6.61%
Urticaria/angioedema	123; 5.42%
21–25 years old (*n* = 3219)	
Atopic dermatits	843; 26.19%
Acne	452; 14.04%
Miscellaneous eczema	407; 12.64%
Urticaria/angioedema	206; 6.4%
Viral wart	179; 5.56%
26–30 years old (*n* = 3516)	
Atopic dermatits	826; 23.49%
Miscellaneous eczema	451; 12.83%
Acne	365; 10.38%
Urticaria/angioedema	230; 6.54%
Viral wart	215; 6.11%
31–35 years old (*n* = 4050)	
Atopic dermatits	824; 20.35%
Miscellaneous eczema	551; 13.6%
Acne	305; 7.53%
Urticaria/angioedema	251; 6.2%
Viral wart	228; 5.63%
36–40 years old (*n* = 3807)	
Atopic dermatits	582; 15.29%
Miscellaneous eczema	503; 13.21%
Urticaria/angioedema	270; 7.09%
Psoriasis	215; 5.65%
Viral wart	203; 5.33%
41–45 years old (*n* = 3298)	
Miscellaneous eczema	454; 13.77%
Atopic dermatits	374; 11.34%
Urticaria/angioedema	248; 7.52%
Tinea pedis	190; 5.76%
Viral wart	175; 5.31%
46–50 years old (*n* = 3201)	
Miscellaneous eczema	453; 14.15%
Tinea pedis	236; 7.37%
Psoriasis	220; 6.87%
Atopic dermatits	215; 6.72%
Urticaria/angioedema	209; 6.53%

Table 5. Top five skin disorders in each age group

51–55 years old (*n* = 4062)	
Miscellaneous eczema	676; 16.64%
Tinea pedis	366; 9.01%
Psoriasis	239; 5.88%
Urticaria/angioedema	239; 5.88%
Tinea unguium	226; 5.56%
56–60 years old (*n* = 5540)	
Miscellaneous eczema	910; 16.43%
Tinea pedis	534; 9.64%
Psoriasis	409; 7.38%
Tinea unguium	331; 5.97%
Urticaria/angioedema	281; 5.07%
61–65 years old (*n* = 5415)	
Miscellaneous eczema	1016; 18.76%
Tinea pedis	519; 9.58%
Tinea unguium	393; 7.26%
Psoriasis	374; 6.91%
Urticaria/angioedema	260; 4.8%
66–70 years old (*n* = 5628)	
Miscellaneous eczema	1141; 20.27%
Tinea pedis	539; 9.58%
Tinea unguium	463; 8.23%
Psoriasis	336; 5.97%
Urticaria/angioedema	250; 4.44%
71–75 years old (*n* = 6157)	
Miscellaneous eczema	1457; 23.66%
Tinea pedis	596; 9.68%
Tinea unguium	566; 9.19%
Psoriasis	327; 5.31%
Seborrheic dermatitis	285; 4.63%
76–80 years old (*n* = 4778)	
Miscellaneous eczema	1304; 27.29%
Tinea pedis	463; 9.69%
Tinea unguium	401; 8.39%
Seborrheic dermatitis	231; 4.83%
Psoriasis	207; 4.33%
81–85 years old (*n* = 2636)	
Miscellaneous eczema	725; 27.5%
Tinea unguium	233; 8.84%
Tinea pedis	230; 8.73%
Herpes zoster/zoster-associated pain	115; 4.36%
Seborrheic dermatitis	93; 3.53%
86–90 years old (*n* = 1099)	
Miscellaneous eczema	307; 27.93%
Tinea unguium	86; 7.83%
Tinea pedis	79; 7.19%
Pressure ulcer	65; 5.91%
Skin ulcer (nondiabetic)	63; 5.73%
91–100 years old (*n* = 427)	
Miscellaneous eczema	110; 25.76%
Pressure ulcer	43; 10.07%
Squamous cell carcinoma/Bowen's disease	35; 8.2%
Skin ulcer (non-diabetic)	28; 6.56%
Bullous pemphigoid	22; 5.15%

Table 6. Sex differences in skin diseases

	Total; Male; Female		Total; Male; Female
Burn	892, 1.33%; 414, 1.34%; 478, 1.32%	Miscellaneous viral disorders	349, 0.52%; 171, 0.55%; 178, 0.49%
Trauma	406, 0.61%; 196, 0.63%; 210, 0.58%	Syphilis	24, 0.04%; 16, 0.05%; 8, 0.02%
Skin ulcer (nondiabetic)	1318, 1.97%; 605, 1.96%; 713; 1.97%	Miscellaneous sexually transmitted diseases	40, 0.06%; 26, 0.08%, 14, 0.04%
Pressure ulcer	606, 0.9%; 313, 1.01%; 293, 0.81%	Bullous pemphigid	509, 0.76%; 208, 0.67%; 301, 0.83%
Miscellaneous physico-chemical skin damage	675, 1.01%; 303, 0.98%; 372, 1.03%	Pemphigus	416, 0.62%; 180, 0.58%; 236, 0.65%
Diabetic dermatoses	432, 0.64%; 300, 0.97%; 132, 0.37%	Miscellaneous bullous diseases	139, 0.21%; 67, 0.22%; 72, 0.2%
Atopic dermatitis	6707, 10.01%; 3486, 11.28%; 3221, 8.92%	Systemic sclerosis	609, 0.91%; 94, 0.3%; 515, 1.43%
Hand eczema	2009, 3%; 532, 1.72%; 1477, 4.09%	Systemic lupus erythematosus	520, 0.78%; 72, 0.23%; 448, 1.24%
Contact dermatitis	2629, 3.92%; 902, 2.92%; 1727, 4.78%	Dermatomyositis	300, 0.45%; 76, 0.25%; 224, 0.62%
Seborrheic dermatitis	2201, 3.28%; 1295, 4.19%; 906, 2.51%	Miscellaneous collagen diseases	911, 1.36%; 209, 0.68%; 702, 1.94%
Miscellaneous eczema	12523, 18.68%; 6289, 20.35%, 6234, 17.26%	Anaphylactoid purpura	169, 0.25%; 72, 0.23%; 97, 0.27%
Urticaria/angioedema	3355, 5.01%; 1251, 4.05%; 2104, 5.82%	Reticular/racemous livedo	80, 0.12%; 21, 0.07%; 59, 0.16%
Prurigo	1216, 1.81%; 755, 2.44%; 461, 1.28%	Miscellaneous vasculitis/purpura/ circulatory disturbance	625, 0.93%; 239, 0.77%; 386, 1.07%
Drug eruption/toxicoderma	1012, 1.51%; 436, 1.41%; 576, 1.59%	Mycosis fungoides	418, 0.62%; 244, 0.79%; 174, 0.48%
Psoriasis	2967, 4.43%; 2138, 6.92%; 829, 2.29%	Miscellaneous lymphomas	283, 0.42%; 149, 0.48%; 134, 0.37%
Palmoplantar pustulosis	828, 1.24%; 284, 0.92%; 544, 1.51%	Pigmented nevus	703, 1.05%; 206, 0.67%; 497, 1.38%
Miscellaneous pustulosis	170, 0.255%; 67, 0.22%; 103, 0.29%	Seborrheic keratosis	1090, 1.63%; 537, 1.74%; 553, 1.53%
Lichen planus	200, 0.3%; 80, 0.26%; 120, 0.33%	Soft fibroma/achrochordon	228, 0.34%; 78, 0.25%; 150, 0.42%
Miscellaneous inflammatory keratotic disorders	241, 0.36%; 95, 0.31%; 146, 0.4%	Epidermal cyst	1183, 1.77%; 713, 2.31%; 470, 1.3%
Tylosis/clavus	911, 1.36%; 292, 0.95%; 619, 1.71%	Lipoma	171, 0.26%; 92, 0.3%; 79, 0.22%
Ichthyosis	61, 0.09%, 31, 0.1%; 30, 0.08%	Dermatofibroma	110, 0.16%; 44, 0.14%, 66, 0.18%
Miscellaneous keratinization disorders	502, 0.75%; 192, 0.62%; 310, 0.86%	Miscellaneous benign skin tumors	1651, 2.46%; 673, 2.18%; 978, 2.71%
Ingrown nail	594, 0.89%; 197, 0.64%; 397, 1.1%	Actinic keratosis	256, 0.38%; 129, 0.42%; 127, 0.35%
Miscellaneous nail disorder	396, 0.59%; 123, 0.4%; 273, 0.76%	Basal cell carcinoma	324, 0.48%; 166, 0.54%; 158, 0.44%
Alopecia areata	1644, 2.45%; 557, 1.8%; 1087, 3.01%	Squamous cell carcinoma/Bowen's disease	447, 0.67%; 272, 0.88%; 175, 0.48%
Androgenic alopecia	208, 0.31%; 198, 0.64%; 10, 0.03%	Paget's disease	221, 0.33%; 136, 0.44%; 85, 0.24%
Miscellaneous skin appendage disorders	266, 0.4%, 77, 0.25%; 189, 0.52%	Malignant melanoma	802, 1.2%; 395, 1.28%; 407, 1.13%
Scabies	96, 0.14%; 50, 0.16%; 46, 0.13%	Miscellaneous malignant skin tumors	531, 0.79%; 291, 0.94%; 240, 0.66%
Insect bite	762, 1.14%; 285, 0.92%; 477, 1.32%	Vitiligo vulgaris	1123, 1.68%; 473, 1.53%; 650, 1.8%
Tinea pedis	4363, 6.51%; 2225, 7.2%; 2138, 5.92%	Chloasma/senile freckle	334, 0.5%; 18, 0.06%; 316, 0.87%
Tinea unguium	3216, 4.8%; 1581, 5.12%; 1635, 4.53%	Miscellaneous pigmented disorders	154, 0.23%; 30, 0.1%; 124, 0.34%
Miscellaneous tinea	607, 0.91%; 404, 1.31%; 203, 0.56%	Erythema multiforme	194, 0.29%; 89, 0.29%; 105, 0.29%
Candidiasis	406, 0.61%; 176, 0.57%; 230, 0.64%	Erythema nodosum	111, 0.17%; 12, 0.04%; 99, 0.27%
Miscellaneous mycosis	209, 0.31%; 117, 0.38%; 92, 0.25%	Miscellaneous disorders with erythematous plaques	130, 0.19%; 40, 0.13%; 90, 0.25%
Acne	2423, 3.62%; 757, 2.45%; 1666, 4.61%	Nevus/phacomatosis (other than pigmented nevus)	266, 0.4%; 89, 0.29%; 177, 0.49%
Impetigo contagiosum	505, 0.75%; 283, 0.92%; 222, 0.61%	Rosacea/rosacea-like dermatitis	148, 0.22%; 36, 0.12%; 112, 0.31%
Folliculitis	749, 1.12%; 432, 1.4%; 317, 0.88%	Granulomatous diseases	192, 0.29%; 65, 0.21%; 127, 0.35%
Erysipelas	81, 0.12%; 35, 0.11%; 46, 0.13%	Keloid/hypertrophic scar	184, 0.27%; 73, 0.24%; 111, 0.31%
Cellulitis	589, 0.88%; 304, 0.98%; 285, 0.79%	Cheilitis/angular cheilitis/mucous membrane diseases	94, 0.14%; 38, 0.12%; 56, 0.16%
Miscellaneous bacterial infection	909, 1.36%; 497, 1.61%; 412, 1.14%	Erythroderma	62, 0.09%; 44, 0.14%; 18, 0.05%
Molluscum contagiosum	602, 0.9%; 327, 1.06%; 275, 0.76%	Other diseases	662, 0.99%; 315, 1.02%; 347, 0.96%
Herpes simplex	688, 1.03%; 266, 0.86%; 422, 1.17%	Total	67 024, 100%; 30 899, 100%; 36 125, 100%
Herpes zoster/zoster-associated pain	1599, 2.39%; 694, 2.25%; 905, 2.51%		
Viral wart	3016, 4.5%; 1388, 4.49%; 1628, 4.51%		

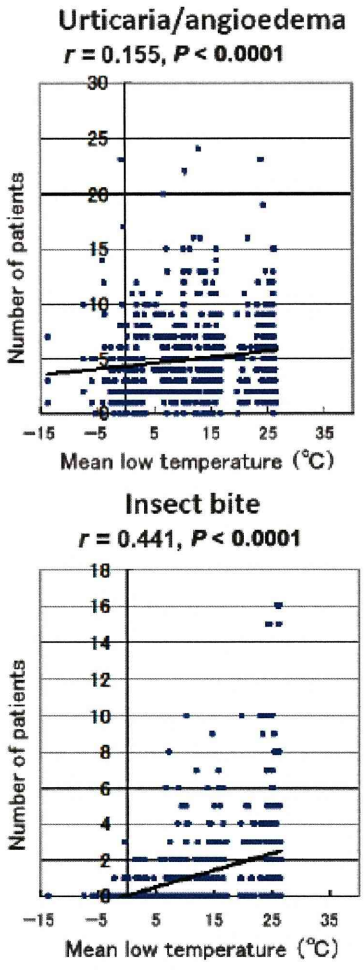

Figure 5. Correlation between patient numbers and mean low temperature in urticaria/angioedema and insect bite.

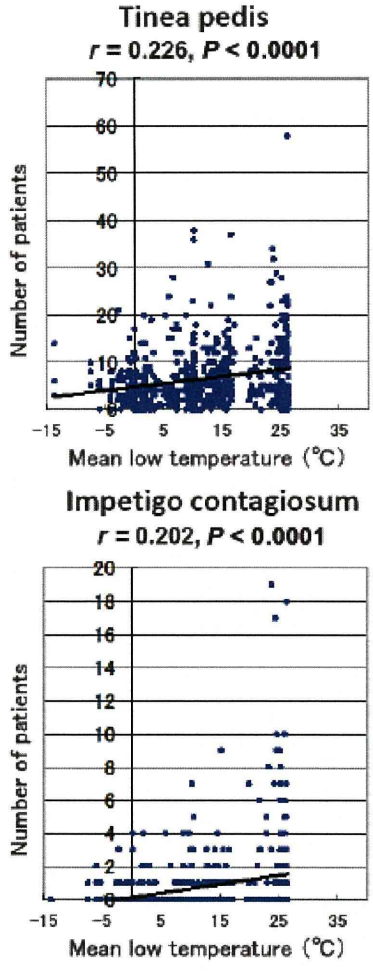

Figure 6. Correlation between patient numbers and mean low temperature in tinea pedis and impetigo contagiosum.

previous hospital-based study in Turkey[3] reported that the five most common disorders were atopic dermatitis, diaper dermatitis, impetigo, seborrheic dermatitis and miliaria in children aged 0–2 years; atopic dermatitis, impetigo, warts, contact dermatitis and insect bites in children aged 3–5 years; contact dermatitis, warts, atopic dermatitis, pruritus and impetigo in children aged 6–11 years; and acne, contact dermatitis, warts, seborrheic dermatitis and pruritus in children aged 12–16 years. For Dutch children aged 0–17 years old in 2001, the incidence rates per person-year of skin disorders were, in descending order, warts 34.3, dermatophytosis 25.4, contact dermatitis/other eczema 22.9, impetigo 20.5, laceration/cuts 20.3, atopic

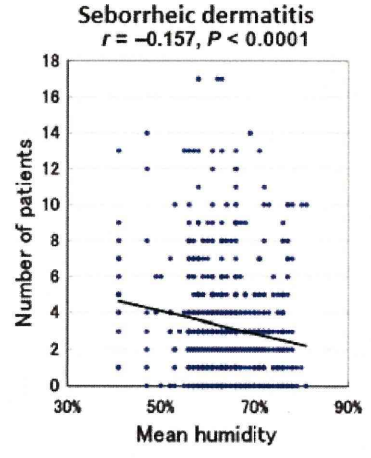

Figure 7. Negative correlation between patient numbers and mean humidity in seborrheic dermatitis.

dermatitis 16.5, moniliasis/candidasis 9.8 and molluscum contagiosum 9.5.[2] Although the order of each disease differed from country to country, atopic dermatitis, miscellaneous eczematous diseases, impetigo and warts appear to share their top rankings in pediatric dermatology, and this was also the case in Japan. Similar observations were also made in 1105 pediatric outpatients aged 0–15 years who visited the hospital of Aarau in Switzerland between 1998 and 2001.[7]

In Turkey, Yalçin *et al.*[8] examined records for 4099 geriatric patients over 65 years old who were admitted to the Ankara Numune Educational and Research Hospital from 1999 through 2003. The five most frequently diagnosed diseases were as follows: in the group aged 65–74 years, eczematous dermatitis, fungal infections, pruritus and bacterial and viral infections; in the group aged 75–84 years, eczematous dermatitis, pruritus, and fungal, viral and bacterial infections; and in the group aged over 85 years, pruritus, eczematous dermatitis, precancerous lesions and skin carcinomas, and viral and fungal infections.[8] In the present study, the Japanese geriatric population was also found to suffer very frequently from miscellaneous eczema and tinea pedis/unguium. In addition, there was a high incidence of psoriasis in elderly Japanese patients. As expected, we found conspicuous differences in the incidence of collagen diseases between the two sexes. A preponderance of collagen diseases in females was also evident in Yalçin's study.[8]

It should be emphasized again that this study was simply a measure of skin disorders in patients attending ordinary dermatology clinics in Japan. The study holds various limitations and biases, but it appears to highlight the current situation regarding patients presenting dermatological problems in Japan.

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CORRESPONDENCE

Angiosarcoma of the forearm arising in an arteriovenous fistula in a renal transplant recipient

Cutaneous angiosarcoma is a rare aggressive malignant tumor with a poor prognosis, usually arising in the scalp of elderly people [1, 2]. Here, we report a very unusual case of angiosarcoma arising in an arteriovenous (AV) fistula in a young renal transplant recipient. To date, 16 cases of angiosarcoma have been published in the setting of organ transplantation, including the present case [3, 4], of which only 9 cases developed in association with an AV fistula. This case probably represents the only case surviving more than 13 months after surgical treatment without any tumor metastasis.

A 40-year-old Japanese man presented with a 3-month history of a painful, easily bleeding tumor on his left thumb. He had received a living-donor renal transplant at the age of 15. Since then, he had been receiving immunosuppressive therapy with corticosteroids and azathioprine. More recently, he had been administrated 5mg corticosteroid every other day and 50 mg azathioprine daily, he had never previously developed any serious skin lesions or tumors on his hand or forearm. The tumor was suspected to have arisen because of obstructed circulation owing to the thrombosed aneurysmal portion (2 cm in size) of an AV fistula on his left forearm; the aneurysmal portion and AV fistula were surgically removed. However, the tumor on the left thumb further enlarged, and the pain exacerbated.

One month later, the patient was referred to our department. Most of the distal portion of his thumb was occupied by an easily bleeding, erythematous to violaceous tumor *(figure 1A)*. Pathological examination of the skin biopsies showed atypical endothelial cell proliferation, indicating angiosarcoma. Magnetic resonance imaging revealed abnormal signal intensity at the distal end of the radius, corresponding to the operative scar overlying the AV fistula; this was suggestive of the existence of angiosarcoma cells. On the basis of these characteristic findings, the condition was diagnosed as angiosarcoma arising in an AV fistula, classified as pT1bN0M0 G4 Stage IIA (soft tissue sarcoma; UICC, 2002).

A below-the-elbow amputation was performed with a 5 cm margin from the operative scar overlying the AV fistula. A multiaxial section of the thumb showed complete necrosis. The adjacent 1.5 cm proximal part was occupied by proliferating atypical endothelial cells forming ill-defined anastomosing channels filled with red blood cells. The tumor cells had enlarged hyperchromatic nuclei with prominent macronuclei and coarse chromatin *(figure 1B)*, and some infiltrated the lower portion of the radius. Immunohistochemical staining showed positivity for CD31, CD34, factor VIII-related antigen, and wide-spectrum cytokeratin (Dako, monoclonal mouse anti-human, clone AE1/AE3). D2-40 and c-kit were absent. These findings were consistent with the typical pathological features of angiosarcoma. Local recurrence or distant metastasis was not observed at the 13-month follow-up. Apart from one Japanese scalp angiosarcoma case after renal plantation [5], this case probably represents the first Asian case arising from AV fistula after renal transplantation.

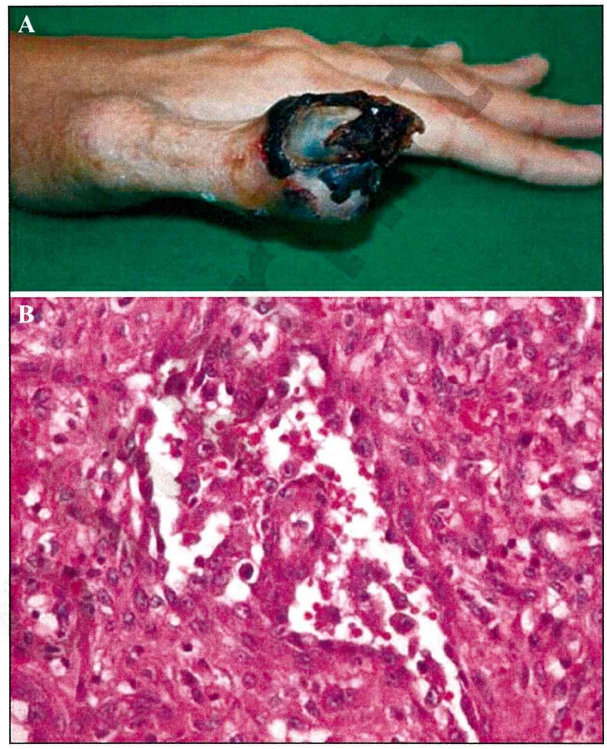

Figure 1. A) Most of the distal portion of the thumb was occupied by an easily bleeding, erythematous to violaceous tumor. **B**) Proliferation of atypical endothelial cells with hyperchromatic nuclei, prominent macronuclei, and coarse chromatin, which are consistent with angiosarcoma (hematoxylin & eosin staining, ×400).

The long-term immunosuppression after renal transplantation and the abnormal blood flow, including altered endothelial milieu caused by aberrant flow dynamics [6], may be responsible for the occurrence of angiosarcoma in an unusual place in this patient.

Table 1 summarizes 9 reported cases for this disease. Interestingly, all these patients were male, but the reason remains unclear. Only 3/9 patients have survived at the time of writing, and all 3 had had amputation with wide margins, *i.e.* 5 cm. This may suggest the importance of early

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Table 1. Reported cases of angiosarcoma arising in an AV fistula (post renal transplantation).

Year	Author	Sex	Age	Treatment	Margin	Outcome
1992	Byers RJ	Male	36	Amp (above-the-elbow)	Unknown	D 12M PO
1993	Keane MM	Male	41	Excision/RT/Chem	n/a	D 8M PO
1993	Conlon PJ	Male	40	Resection/RT	n/a	D 5M PO
1996	Medioni LD	Male	60	Amp	n/a	D 11M PO
1998	Wehrli BM	Male	71	Amp (below-the-elbow)	Widely free	Survival (at 6M PO)
1998	Bessis D	Male	68	Amp (above-the-elbow)	Unknown	D 7M PO
2005	Farag R	Male	39	Resection	n/a	D 11M PO
2010	Qureshi YA	Male	48	Amp (above-the-elbow)	Free (5cm)	Survival (at 9M PO)
2011	This case	Male	40	Amp (below-the-elbow)	Free (5cm)	Survival (at 13M PO)

Year: reported year; Age: age at diagnosis; RT: radio therapy; Chem: chemotherapy; n/a: not applicable; Amp: amputation; D: dead; M: month; PO: post operation.

amputation with sufficient margins for this disease, when applicable. This case alerts dermatologists to the possibility of an increase in non-scalp angiosarcoma in the future, as the number of renal transplant patients has drastically increased world wide recently. ■

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