the technical staff of the Center for Genomic Medicine for providing technical assistance and K. Barrymore for proofreading this manuscript. This work was supported by Health Science Research Grants from the Ministry of Health, Welfare and Labor of Japan and the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References

[1] Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361:496–509.
[2] Sonnenberg GF, Fouser LA, Artis D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. Nat Immunol 2011;12:383–90.
[3] Ma HL, Liang S, Li J, Napierata L, Brown T, Benoit S, et al. IL-22 is required for Th17 cell-mediated pathology in a mouse model of psoriasis-like skin inflammation. J Clin Invest 2008;118:597–607.
[4] Wolk K, Witte E, Wallace E, Döcke WD, Kunz S, Asadullah K, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. Eur J Immunol 2006;36:1309–23.
[5] Boniface K, Guignouard E, Pedretti N, Garcia M, Delwail A, Bernard FX, et al. A role for T cell-derived interleukin 22 in psoriatic skin inflammation. Clin Exp Immunol 2007;150:407–15.
[6] Koga C, Kabashima K, Shiraishi N, Kobayashi M, Tokura Y. Possible pathogenic role of Th17 cells for atopic dermatitis. J Invest Dermatol 2008; 128:2625–30.
[7] Shimizu M, Matsuda A, Yanagisawa K, Hirota T, Ahahoshi M, Inomata N, et al. Functional SNPs in the distal promoter of the ST2 gene are associated with atopic dermatitis. Hum Mol Genet 2005;14:2919–27.
[8] Weger W, Hofer A, Wolf P, El-Shabrawi Y, Renner W, Kerl H, et al. Common polymorphisms in the interleukin-22 gene are not associated with chronic plaque psoriasis. Exp Dermatol 2009;18:796–8.
[9] Tsoi LC, Spain SL, Knight J, Ellinghaus E, Stuart PE, Capon F, et al. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nat Genet 2012;44:1341–8.
[10] Wilsmann-Theis D, Hagemann T, Jordan J, Bieber T, Novak N. Facing psoriasis and atopic dermatitis: are there more similarities or more differences? Eur J Dermatol 2008;18:172–80.

Hidehisa Saeki[a,1,*], Tomomitsu Hirota[b,1], Hidemi Nakagawa[a], Yuichiro Tsunemi[c], Toyoaki Kato[d], Sayaka Shibata[d], Makoto Sugaya[d], Shinichi Sato[d], Satoru Doi[e], Akihiko Miyatake[f], Kouji Ebe[g], Emiko Noguchi[h], Tamotsu Ebihara[i], Masayuki Amagai[i], Hitokazu Esaki[j], Satoshi Takeuchi[j], Masutaka Furue[j], Yusuke Nakamura[k], Mayumi Tamari[b]

[a]*Department of Dermatology, The Jikei University School of Medicine, Japan*; [b]*Laboratory for Respiratory Diseases, Center for Genomic Medicine, RIKEN, Japan*; [c]*Department of Dermatology, Tokyo Women's Medical University, Japan*; [d]*Department of Dermatology, Faculty of Medicine, University of Tokyo, Japan*; [e]*Osaka Prefectual Medical Center for Respiratory and Allergic Diseases, Japan*; [f]*Miyatake Asthma Clinic, Japan*; [g]*Takao Hospital, Japan*; [h]*Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan*; [i]*Department of Dermatology, Keio University School of Medicine, Japan*; [j]*Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Japan*; [k]*Institute of Medical Science, The University of Tokyo, Japan*

*Corresponding author at: Department of Dermatology, The Jikei University School of Meicine, 3-25-8, Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan.
Tel.: +81 3 3433 1111; fax: +81 3 5401 0125
E-mail address: saeki-der@jikei.ac.jp (H. Saeki)

[1]These authors contributed equally to this article.

1 March 2013

http://dx.doi.org/10.1016/j.jdermsci.2013.04.002

Letter to the Editor

HLA-B*58:01 strongly associates with allopurinol-induced adverse drug reactions in a Japanese sample population

To the Editor,

Allopurinol, an inhibitor of xanthine oxidase, is widely used for the treatment of hyperuricemia associated with chronic gout, acute uric acid nephropathy, recurrent uric acid stone formation, certain enzyme/blood disorders, and cancer chemotherapy. It has been shown that severe cutaneous adverse drug reactions (ADRs) caused by allopurinol were strongly associated with HLA-B*58:01 in a Han Chinese sample population [1]. Odds ratio (OR) for the association of HLA-B*58:01 with allopurinol-induced severe cutaneous ADR in this population was 580.3 and 95% CI was 34.4–9780.9. Although the relationship between HLA-B*58:01 and allopurinol-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) has subsequently been studied in European and Japanese patients, the association was much weaker than that reported in Han Chinese patients [2,3]. The association study in Japanese patients was examined in only a limited number of allopurinol-induced ADR cases. We therefore conducted a case-controlled study to determine HLA types associated with allopurinol-induced ADR in a Japanese sample population.

All patients were recruited from Shimane University Hospital between 2010 and 2012. These included 7 patients with allopurinol-induced ADR (3 patients with SJS and 4 patients with erythema exudativum multiforme (EEM)) and 25 patients who had been receiving allopurinol for more than 3 months without drug eruption. Diagnoses of SJS were made according to the diagnostic criteria established by Roujeau [4]. Allopurinol-induced ADR was diagnosed using medical histories, indicating that symptoms occurred within 3 months of starting allopurinol administration, and the symptoms resolved upon the withdrawal of allopurinol. If the patients were given other drugs, in addition to allopurinol, 3 months prior to the appearance of symptoms, a drug-induced lymphocyte stimulation test and a patch test were performed with allopurinol/oxypurinol. Allopurinol-induced ADRs were diagnosed by the single medication of allopurinol in 4 of the 7 patients (No. 1, 3, 4, 7), by the positive allopurinol-induced lymphocyte stimulation test in 2 of the 7 patients (No. 2, 6), and by the positive patch test with allopurinol in the patient No. 5. The indication for which drug had been prescribed was the level of hyperuricemia detected in all the patients. All patients were interviewed by investigators regarding the histories of their biological parents and grandparents, and were confirmed as being ethnically Japanese. This study was approved by the ethics committee of Shimane University Faculty of Medicine (approval no. 221).

Low-resolution HLA typing with DNA extracted from peripheral blood was performed using the reverse sequence-specific oligonucleotide with polymerase chain reaction (PCR-rSSO) method [5]. High-resolution HLA-B genotyping was determined using the polymerase chain reaction-sequence based typing (PCR-SBT) method [5]. Statistical analysis of the differences in each allele frequency among patients with ADR and control subjects was performed by Fisher's exact test. The strength of association was estimated by calculating the OR. The OR was determined using Haldane's modification, which adds 0.5 to all cells to accommodate

Table 1
HLA DNA typing of allopurinol-induced ADR patients.

No.	Age/sex	Type of ADR	Low-resolution HLA DNA typing					
1	88/F	SJS	A2	A33	B61	B58	DR9	DR9
2	72/M	SJS	A2	A24	B59	B58	DR4	DR13
3	70/M	SJS ocular type[a]	A24	A26	B37	B55	DR8	DR14
4	78/M	EEM minor	A2	A24	B52	B58	DR4	DR13
5	75/F	EEM minor	A2	A26	B13	B62	DR4	DR12
6	65/M	EEM minor	A2	A26	B35	B35	DR8	DR15
7	67/M	EEM minor	A24	A33	B58	B58	DR13	DR15

[a] SJS ocular type: SJS without eruption but corneal erosion with pseudomembrane formation.

possible zero counts. We used Statistical SPSS statistical package, version 20.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis. All reported *P*-values were two-sided. Values of $P < 0.05$ were considered to be statistically significant.

Low resolution HLA DNA typing of allopurinol-induced ADR patients were shown in Table 1. Of the seven patients with allopurinol-induced ADR, two SJS, and two EEM patients had HLA-B58, whereas no allopurinol-tolerated patients had HLA-B58. The high resolution HLA DNA typing revealed that all patients with HLA-B58 were HLA-B*58:01. Comparing the frequency of each type between the allopurinol-induced ADR patients and the allopurinol-tolerant patients, the OR of HLA-B*58:01 was significantly high in the allopurinol-induced ADR patients, as shown in Table 2. The OR of HLA-B*58:01 was the highest and reached to 65.6. The 95% CI was 2.9 to 1497.0. When compared, the OR was 26.0 and the 95% CI was 2.0 to 336.1 (table not shown) between the 4 EEM minor patients and the allopurinol-tolerant patients.

In this study we confirmed the association between HLA-B*58:01 and allopurinol-induced ADR in a Japanese sample population and established the OR of 65.6. This is compatible with the results reported by Tohkin et al. [3], and meta-analysis reported by Somkrua et al. that the risk of developing SJS/TEN among those allopurinol users with HLA-B*5801 was significantly increased by 34–348 times compared to those without the gene [6]. In addition, we confirmed an association between HLA-B*58:01 and allopurinol-induced EEM minor, which is mild type of ADR. Thus indicating that HLA-B*58:01 is associated with the pathogenesis of allopurinol-induced ADR, regardless of the type of severity of ADR. The present study support the assertion that HLA-B*58:01 is a susceptibility gene for allopurinol-induced ADR regardless of populations, although some difference in the

Table 2
Statistical analysis in HLA typing of allopurinol-induced ADR patients and allopurinol-tolerant patients.

HLA low-resolution	Allopurinol-tolerant patients ($n=25$)	Allopurinol-induced ADR patients ($n=7$)	OR[b]	95% CI	*P*-value[a]	HLA gene frequencies in Japanese ($n=371$)
A2	11	5	2.8	0.5–14.9	0.394	0.222
A11	5	0	0.2	0.0–5.1	0.560	0.083
A24	12	4	1.4	0.3–6.8	1.000	0.380
A26	9	3	1.4	0.3–6.8	1.000	0.130
A31	2	0	0.6	0.0–14.6	1.000	0.071
A33	5	2	1.7	0.3–9.9	0.632	0.097
B7	1	0	1.1	0.0–29.6	1.000	0.065
B13	0	1	11.8	0.4–323.7	0.219	0.018
B35	8	1	0.5	0.0–3.4	0.640	0.076
B37	0	1	11.8	0.4–323.7	0.219	0.013
B39	1	0	1.1	0.0–29.6	1.000	0.050
B44	5	0	0.2	0.0–5.1	0.560	0.075
B46	1	0	1.1	0.0–29.6	1.000	0.039
B48	1	0	1.1	0.0–29.6	1.000	0.037
B51	2	0	0.6	0.0–14.5	1.000	0.101
B52	3	1	1.5	0.2–12.1	1.000	ND[c]
B54	6	0	0.2	0.0–4.0	0.296	0.036
B55	1	1	3.8	0.3–42.5	0.395	0.022
B56	1	0	1.1	0.0–29.6	1.000	0.006
B58	0	4	65.6	2.9–1497.0	9.733×10^{-4}	0.004
B59	1	1	3.8	0.3–42.5	0.395	0.018
B60	2	0	0.6	0.0–14.6	1.000	ND[c]
B61	5	1	0.9	0.1–6.4	1.000	ND[c]
B62	3	1	1.5	0.2–12.1	1.000	ND[c]
B67	3	0	0.4	0.0–9.3	1.000	0.003
B71	2	0	0.6	0.0–14.6	1.000	ND[c]
B75	1	0	1.1	0.0–29.6	1.000	ND[c]
DR1	2	0	0.6	0.0–14.6	1.000	0.065
DR4	17	3	0.4	0.0–1.9	0.379	0.225
DR8	3	2	2.9	0.5–19.0	0.296	0.121
DR9	7	1	0.6	0.0–4.1	0.646	0.012
DR12	1	1	3.8	0.3–42.5	0.395	0.051
DR13	5	3	2.9	0.5–15.6	0.327	0.084
DR14	4	1	1.1	0.1–8.5	1.000	0.090
DR15	5	2	1.7	0.3–9.9	0.632	0.185
DR16	3	0	0.4	0.0–9.3	1.000	0.009

[a] *P*-value: Fisher's exact test.
[b] OR: determined using Haldone's modification, which adds 0.5 to all cells to accommodate possible zero counts.
[c] ND: no data.

ORs are seen among ethnic populations. This is in contrast to carbamazepine-induced ADR with which HLA types associated vary among ethnic populations [5]. A strong association between HLA-B*1502 and carbamazepine-induced ADRs was found in Han Chinese, Thai, Malaysian and Indian sample populations [5,7]. However, recent studies have revealed an association between carbamazepine-induced ADRs and HLA-A*31:01 in Caucasian and Japanese sample populations [5]. These findings indicate that severe cutaneous ADRs induced by allopurinol as well as carbamazepine could be prevented if such genetic information would be known a *priori*. In fact, cost-effectiveness of HLA-B*1502 allele screening before prescription of carbamazepine has recently been reported [8]. Thus the development of a simple and rapid genotyping methods for these susceptibility genes are desirable.

Acknowledgment

This work supported in part by Health and Labour Sciences Research Grants (Research on Intractable Diseases) from the Japanese Ministry of Health, Labour and Welfare.

References

[1] Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005;102:4134–9.
[2] Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al. A European study of HLA-B in Stevens–Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008;18: 99–107.
[3] Tohkin M, Kaniwa N, Saito Y, Sugiyama E, Kurose K, Nishikawa J, et al. A whole-genome association study of major determinants for allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis in Japanese patients. Pharmacogenomics J 2013;13:60–7.
[4] Roujeau JC. The spectrum of Stevens–Johnson syndrome and toxic epidermal necrolysis: a clinical classification. J Invest Dermatol 1994;102:28–30.
[5] Niihara H, Kakamu T, Fujita Y, Kaneko S, Morita E. HLA-A31 strongly associates with carbamazepine-induced adverse drug reactions but not with carbamazepine-induced lymphocyte proliferation in a Japanese population. J Dermatol 2012;39:594–601.
[6] Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Med Genet 2011;12:118, http://www.biomedcentral.com/1471-2350/12/118.
[7] Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens–Johnson syndrome. Nature 2004;428:486.
[8] Dong D, Sung C, Finkelstein EA. Cost-effectiveness of HLA-B*1502 genotyping in adult patients with newly diagnosed epilepsy in Singapore. Neurology 2012;18: 1259–67.

Hiroyuki Niihara[a,*], Sakae Kaneko[a], Takahumi Ito[b], Takashi Sugamori[c], Nobuyuki Takahashi[c], Kunie Kohno[d], Eishin Morita[a]

[a]*Department of Dermatology, Faculty of Medicine, Shimane University, Izumo, Japan*
[b]*Section of Nephrology, Department of Internal Medicine, Faculty of Medicine, Shimane University, Izumo, Japan*
[c]*Section of Cardiovascular Internal Medicine, Department of Internal Medicine, Faculty of Medicine, Shimane University, Izumo, Japan*
[d]*Center for Community-Based Health Research and Education (COHRE), Organization for the Promotion of Project Research, Shimane University, Izumo, Japan*
*Corresponding author at: Department of Dermatology, Faculty of Medicine, Shimane University, 89-1 Enya-cho, Izumo 693-8501, Shimane, Japan.
Tel.: +81 853 202 210; fax: +81 853 218 317

E-mail addresses: ofcourse@med.shimane-u.ac.jp
niiharahiroyuki@gmail.com (H. Niihara)

22 November 2012

http://dx.doi.org/10.1016/j.jdermsci.2013.04.013

gene-related peptide, which is the mediator of pruritus, and modulate the μ-opioid receptor making it possible to change the sensorium of pruritus.[1,3,4] Pregabalin shows faster treatment response than gabapentin and it does not bind to plasma protein, so has the advantage of use in patients with low plasma protein and hepatic failure.[3]

Our study has several limitations. First, this was an open-label uncontrolled study and the effect of pregabalin could be attributed to a placebo effect. Second, we used pregabalin in a fixed dose of 150 mg/day. It is known that pregabalin may be used in higher doses up to 300 mg/day within 1 week based on efficacy and tolerability. Third, pregabalin also works for underlying neuropathic pain and anxiety, and so it could affect these accompanying symptoms and may lead to an overall improvement.

ACKNOWLEDGMENT

This study was supported by a Medical Research Institute Grant (2011-5) from Pusan National University Hospital.

Jung-Min PARK, Seung-Wook JWA, Margaret SONG, Hoon-Soo KIM, Hyun-Chang KO, Moon-Bum KIM, Kyung-Sool KWON, Byung-Soo KIM
Department of Dermatology, Pusan National University School of Medicine, and Biomedical Research Institute, Pusan National University Hospital, Busan, Korea

REFERENCES

1 Yesudian PD, Wilson NJE. Efficacy of gabapentin in the management of pruritus of unknown origin. *Arch Dermatol* 2005; **141**: 1507–1509.
2 Nakamizo S, Miyachi Y, Kabashima K. Treatment of neuropathic itch possibly due to trigeminal trophic syndrome with 0.1% topical tacrolimus and gabapentin. *Acta Derm Venereol* 2010; **90**: 654–655.
3 Ehrchen J, Stander S. Pregabalin in the treatment of chronic pruritus. *J Am Acad Dermatol* 2008; **58**: S36–S37.
4 Porzio G, Proto C, Tudini M. Efficacy of pregabalin in the management of cetuximab-related itch. *J Pain Symptom Manage* 2006; **32**: 397–398.

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

Correspondence: Kazuo Mizumoto, M.D., Department of Dermatology, Masuda Medical Association Hospital, 2-1917 Toda-cho, Masuda, Shimane 699-3637, Japan. Email: k-mizumoto@masumi.shimane.med.or.jp

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 (–)

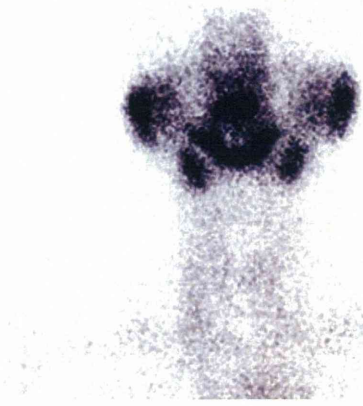

Figure 1. No uptake of technetium-99*m* was identified in the thyroid. F-T3 and FT-4 were high and thyroid-stimulating hormone was suppressed. Furthermore, anti-thyroid antigen did not appear. We then made a diagnosis of indolent thyroiditis.

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.

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 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.

ACKNOWLEDGMENTS

This work was partly supported by Health and Labor Sciences Research Grants (Research on Intractable Diseases) from the Ministry of Health, Labor and Welfare of Japan.

Kazuo MIZUMOTO,[1] Yasuyuki SUMIKAWA,[2] Hiroyuki NIIHARA,[2] Eishin MORITA[2]

[1]*Department of Dermatology, Matsue City Hospital, and* [2]*Department of Dermatology, Shimane University Faculty of Medicine, Shimane, Japan*

REFERENCES

1 Mallal S, Phillips E, Carosi G *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568–579.
2 Kaniwa N, Saito Y, Aihara M *et al.* HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 2008; **9**: 1617–1622.
3 Hung SI, Chung WH, Jee SH *et al.* Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006; **16**: 297–306.
4 Ozeki T, Mushiroda T, Yowang A *et al.* Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet* 2011; **20**: 1034–1041.

Successful treatment with adapalene of cetuximab-induced acneiform eruptions

Dear Editor,

The epidermal growth factor receptor (EGFR) has been identified as a new target for the treatment of many human solid tumors. EGFR is involved in normal cell growth and differentiation in non-malignant cells such as epidermal keratinocytes, sebocytes and hair follicles. Cetuximab is a chimeric monoclonal antibody that selectively binds to the EGFR, blocking its activation and signal transduction. Cetuximab is approved for use in EGFR-expressing colorectal cancer in patients previously resistant to chemotherapy.[1] The most common adverse effects of cetuximab are cutaneous

Correspondence: Atsushi Fukunaga, M.D., Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017 Japan. Email: atsushi@med.kobe-u.ac.jp

EL27—2　重症薬疹のトピックス

ウイルス感染と重症薬疹

浅田　秀夫

はじめに

ウイルス感染がアレルギーの発症や経過に影響をおよぼすことは以前から知られている．たとえば，EBウイルスによる伝染性単核症にアンピシリンを投与すると，しばしば薬疹が出現するが，この現象はアンピシリン疹として有名である．近年，多臓器障害を伴う重症型薬疹のひとつであるdrug-induced hypersensitivity syndrome（DIHS）において，HHV-6などのヒトヘルペスウイルスの再活性化がみられることが明らかとなってきた[1)2)]．即ち，薬疹は投与された薬剤によるアレルギー反応と考えられてきたが，その発症にウイルス感染が広く影響をおよぼしている可能性を示すデータが集積しつつある．本講演では，ウイルス感染症との関係が強く疑われている薬疹について代表的なものを取り上げて，ウイルス感染がその発症に果たす役割について解説する．さらに，造血幹細胞移植後のgraft versus host disease（GVHD）におけるHHV-6の再活性化についてわれわれの知見を紹介し，DIHSとの類似性についても言及する．

ウイルス感染症が関与する薬疹

ウイルス感染症と薬疹との関わりは大きく2つのグループに大別される．一つはウイルス感染が先行し引き続き薬疹を生じるタイプで，このグループに属するものとしては，伝染性単核症に併発するアンピシリン疹が有名であるが，そのほかヒト免疫不全ウイルス（HIV）感染症患者にみられる薬疹などもあげられる．もう一つは，薬剤によりウイルスの再活性化が引き起こされるタイプで，このグループの代表がDIHSである．

1．ウイルス感染が薬疹に先行するタイプ

●HIV感染症と薬疹

HIV感染症の患者では，CD4＋T細胞数が減少し，免疫不全症状がみられる．その一方で，薬疹の多発や虫刺症の著明な増悪などのアレルギー症状が目立つようになる．アモキシシリンやサルファ剤に対する薬疹は，非感染者より約10倍多いとされる[3)]．カリニ肺炎の予防・治療に用いられるST合剤に対しては，約50％の感染者が薬疹を生ずる．薬疹のタイプは紅斑丘疹型が多いが，toxic epidermal necrolysis（TEN）型の頻度も健常群と比べて高率にみられる（図1）[4)]．興味深いことに，病期が進みCD4＋T細胞が減少する程，薬疹の頻度や重症度が増すことが知られている[5)]．その理由として，HIVにより免疫を制御しているCD4＋T細胞（Regulatory T cell：Treg）の減少や機能低下が著しく起こり，その結果，アレルギー反応がむしろ増強するとの報告がみられる[6)]．また，HIV感染患者では，EBV，サイトメガロウイルス，HHV-6, HHV-7などの様々なウイルスの再活性化がみられ，それらのウイルスの薬疹発症への関与も疑われている．その他，HIV感染患者では，薬物代謝に関わるグルタチオンの欠乏や薬物のアセチル化の遅延[7)]が高頻度にみられるため，薬物の中間代謝産物が毒性を発揮したり，アレルギー反応を引き起こすことも一因ではないかと考えられている．

2．薬剤によりウイルスの再活性化が引き起こされるタイプ

●DIHSとHHV-6

DIHSとは，薬剤投与開始から3週～6カ月で遅発性に発症し，多臓器障害を伴う重症型薬疹のひとつである．皮疹は，紅斑丘疹型（時に多形紅斑型）に始まって紅皮症となることが多い．皮疹だけでなく，リンパ節腫脹，発熱，異型リンパ球の出現や好酸球の増多，肝障害などの症状を認め，しばしば原因薬剤の中止後も，皮疹や臓器障害が遷延する．近年，発症後2～4週後にHHV-6の再活性化を伴うことが判明し，薬剤アレルギーとウイルス感染症の複合した新たな病態として認識されるようになった．

われわれは最近，DIHS急性期に血清TARC値が著しく高値（平均20,000 pg/ml以上）を示すことを見出した（図2）[8)]．TARCはTh2細胞を誘導するケモカイ

奈良県立医科大学皮膚科学
〒634-8521 奈良県橿原市四条町840
【別刷請求先】浅田秀夫
奈良県立医科大学皮膚科学
〒634-8521 奈良県橿原市四条町840
電話：0744-29-8890　FAX：0744-25-8511
e-mail：asadah@naramed-u.ac.jp

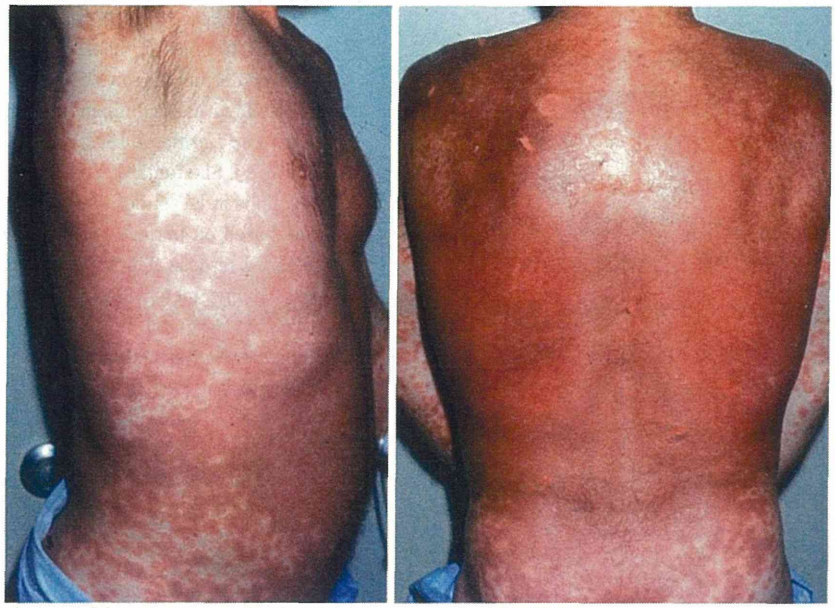

図1　ST合剤によるTEN型薬疹.

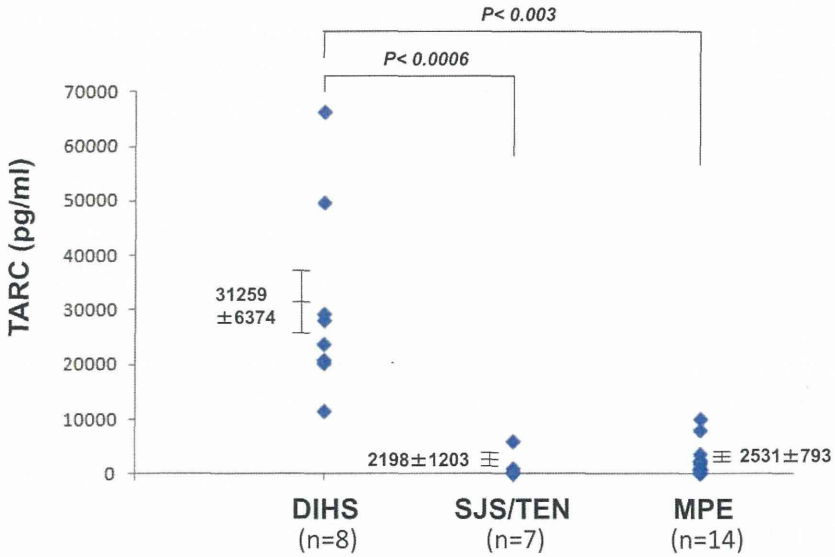

図2　DIHS，SJS/TEN，MPE（紅斑丘疹型薬疹）の急性期における血清TARC値の比較.

ンの一つで，現在，アトピー性皮膚炎の重症度マーカーとして広く使用されている．TARCの上昇はDIHSに特徴的で，一般の紅斑丘疹型薬疹やStevens-Johnson/TENでは中等度の上昇を示すのみである（平均2,000 pg/ml）．さらに，HHV-6再活性化を伴わないDIHS類似の薬疹と比べても，HHV-6再活性化を伴う真のDIHSにおいて有意に高値を認めたことから，HHV-6の再活性化に関わっている可能性が推測される．

GVHDにおけるHHV-6の再活性化—DIHSの病態モデル？

われわれは，GVHDとヒトヘルペスウイルス再活性化との関連性を調べる目的で，移植前ならびに移植後経時的に，末梢血中のヒトヘルペスウイルス（HHV-6, HHV-7, EBV，CMV）DNAの定量を行い，GVHDとの関係を検討した[9]．その結果，移植患者15例中，GVHDを発症した10例全例にHHV-6の再活性化を認め，そのうち8例では発疹の出現・消退と血中HHV-6 DNAレベルとの間に相関がみられた．一方，GVHDを発症しなかった5例の内HHV-6 DNAが検

出されたのは1例のみで，また，HHV-6以外のヒトヘルペスウイルスとGVHDとの相関はみられなかった．さらに，発疹の出現に一致して，血清中IL-10と可溶性IL-2受容体の上昇も認められた．以上のことから，造血幹細胞移植後のGVHDの発症にはHHV-6の再活性化とIL-10産生T細胞の活性化が密接に関わっているものと考えられた．

以上の結果から，GVHDとDIHSとの間には，皮膚症状，発熱，臓器障害，HHV-6再活性化，IL-10産生T細胞の活性化など，多くの共通点があり，GVHDがDIHSの病態モデルとなり得る可能性が示唆された．

文献

1) Suzuki Y, Inagi R, Aono T, et al: Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. *Arch Dermatol*, 1998; 134: 1108–1112.
2) Tohyama M, Yahata Y, Yasukawa M, et al: Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. *Arch Dermatol*, 1998; 134: 1113–1117.
3) Coopman SA, Johnson RA, Platt R, et al: Cutaneous disease and drug reactions in HIV infection. *N Engl J Med*, 1993; 328: 1670–1674.
4) Saiag P, Caumes E, Chosidow O, et al: Drug-induced toxic epidermal necrolysis (Lyell syndrome) in patients infected with the human immunodeficiency virus. *J Am Acad Dermatol*, 1992; 26: 567–574.
5) Smith KJ, Skelton HG, Yeager J, et al: Increased drug reactions in HIV-1-positive patients:a possible explanation based on patterns of immune dysregulation seen in HIV-1 disease, The Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). *Clin Exp Dermatol*, 1997; 22: 118–123.
6) Eggena MP, Barugahare B, Jones N, et al: Depletion of regulatory T cells in HIV infection is associated with immune activation. *J Immunol*, 2005; 174: 4407–4414.
7) Rieder MJ, Shear NH, Kanee A, et al: Prominence of slow acetylator phenotype among patients with sulfonamide hypersensitivity reactions. *Clin Pharmacol Ther*, 1991; 49: 13–17.
8) Ogawa K, Morito H, Hasegawa A, et al: Identification of thymus and activation-regulated chemokine (TARC/CCL17) as a potential marker for early indication of disease and prediction of disease activity in drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS). *J Dermatol Sci*, 2013; 69: 38–43.
9) Kitamura K, Asada H, Iida H, et al: Relationship among human herpesvirus 6 reactivation, serum interleukin 10 levels, and rash/graft-versus-host disease after allogeneic stem cell transplantation. *J Am Acad Dermatol*, 2008; 58: 802–809.

CED
Clinical and Experimental Dermatology

CPD

Increased ratio of FoxP3+ regulatory T cells/CD3+ T cells in skin lesions in drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms

H. Morito,[1] K. Ogawa,[1] T. Fukumoto,[1] N. Kobayashi,[1] T. Morii,[2] T. Kasai,[3] A. Nonomura,[3] T. Kishimoto[4] and H. Asada[1]

[1]Department of Dermatology, Nara Medical University School of Medicine, Nara, Japan; [2]Second Department of Internal Medicine, Nara Medical University School of Medicine, Nara, Japan; [3]Department of Diagnostic Pathology, Nara Medical University School of Medicine, Nara, Japan; and [4]Department of Psychiatry, Nara Medical University School of Medicine, Nara, Japan

doi:10.1111/ced.12246

Summary

Background. Drug-induced hypersensitivity syndrome/drug rash with eosinophilia with systemic symptoms (DIHS/DRESS) is a severe drug eruption accompanied by multiorgan disorders. Several unique aspects of DIHS/DRESS, including reactivation of herpesvirus, liver dysfunction and hypogammaglobulinemia, have similarities to graft-versus-host disease (GVHD).

Aim. In this study, we focused on the dynamics of regulatory T cells (Tregs) infiltrating into the skin lesions of DIHS/DRESS and GVHD.

Methods. Skin biopsies were taken from patients with DIHS/DRESS, GVHD, or maculopapular drug eruption. Tregs were detected using immunostaining with anti-FoxP3.

Results. The ratio of FoxP3+ T cells to CD3+ T cells was significantly higher in the skin lesions of DIHS/DRESS than in those of patients with GVHD and was positively correlated with the number of days from disease onset in the acute phase.

Conclusions. The dynamics of Tregs in skin lesions are different between DIHS/DRESS and GVHD, despite there being many similarities between these conditions.

Introduction

Drug-induced hypersensitivity syndrome/drug rash with eosinophilia with systemic symptoms (DIHS/DRESS) is a severe drug eruption accompanied by multiorgan disorders.[1] It may be related to reactivation of human herpesvirus (HHV), especially HHV-6,[2–4] and to mild epidermal injury, in contrast to other severe adverse cutaneous drug reactions such as toxic epidermal necrosis (TEN) and Stevens–Johnson syndrome (SJS). However, the mechanisms of HHV reactivation and development of drug rashes are currently unknown. DIHS/DRESS has several notable features, such as delayed onset, worsening of clinical symptoms even after withdrawal of the causative drug, hypogammaglobulinemia,[5] reactivation of latent HHV during the acute stage of the disease, and autoimmune complications developing as short-term or long-term sequelae, such as autoimmune thyroiditis, positive reaction of antinuclear antibodies and fulminant type 1 diabetes mellitus.[6,7] Many aspects of this syndrome suggest close similarities between DIHS/DRESS and graft-versus-host disease (GVHD). We and other researchers have also revealed a relationship between HHV-6 reactivation and rash/GVHD after allogeneic stem cell transplantation,[8,9] Various complications frequently occurring in GVHD, such as autoimmune disease,[10,11] are frequently observed during the course of DIHS/DRESS, even long after its clinical resolution. However, there are clinical and histological differences

Correspondence: Dr Hideo Asada, Department of Dermatology, Nara Medical University School of Medicine, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
E-mail: asadah@naramed-u.ac.jp

Conflict of interest: None declared.

Accepted for publication 7 July 2013

between DIHS/DRESS and GVHD; for example, interface dermatitis and apoptotic keratinocytes can be observed in both DIHS/DRESS and GVHD, but are more severe in the latter.

Recently, much attention has been focused on regulatory T cells (Tregs) and their roles in drug eruption/GVHD. However, the dynamics of Tregs in the skin lesions in DIHS/DRESS and GVHD are not fully understood. In this study, we focused on the dynamics of Tregs infiltrating into the skin, one of the major target organs in DIHS/DRESS and GVHD, to examine the involvement of Tregs in the development of DIHS/DRESS and GVHD skin lesions.

Methods

The study was approved by the medical ethics committee of Nara Medical University, and all patients gave informed consent.

Patients and samples

Our study consisted of three groups of patients: patients with DIHS/DRESS ($n = 12$), patients with acute GVHD ($n = 12$) and patients with maculopapular drug eruption (MDE) ($n = 18$). The eliciting drugs had been withdrawn by the time of diagnosis of DIHS/DRESS or drug eruption in all patients.

The DIHS/DRESS group consisted of 12 patients (5 men, 7 women; median age 59 years, range 13–75) who were enrolled consecutively during the period April 2003. The profiles of these patients are shown in Table 1. Diagnosis of DIHS/DRESS was based on criteria established by a Japanese consensus group[12] and by RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions).[13] Reactivation of HHV, including HHV-6 and HHV-7, was demonstrated by an increase in the titre of the specific serum IgG antibody and/or DNA levels in whole blood as detailed below. Skin biopsies were also taken from areas of maculopapular erythema in this group.

Table 2 details the characteristics of 12 consecutive patients with clinical signs of acute GVHD (3 men, 9 women; median age 52 years, range 7–66) who received allogeneic stem cell transplantation for haematological malignancy during the period November 2002 to August 2011. All 12 patients had received standard prophylaxis (ciclosporin in 10 patients and mycophenolate mofetil in 2 patients) prior to transplantation. Skin biopsies were taken from areas of erythematous maculopapular rash in all 12 patients, which were clinically graded according to standard criteria.[14]

The final group consisted of 18 patients (10 men, 8 women; median age 61 years, range 32–81). Skin biopsies were also taken from areas of cutaneous rash of patients without allografts or DIHS/DRESS ($n = 18$) that was clinically and histopathologically considered to be an MDE.

Assessment of herpesvirus DNA

DNA levels were assessed by PCR. DNA was extracted from whole blood using a commercial kit (QIAamp DNA Blood Mini-kit; Qiagen Inc., Tokyo, Japan) in accordance with the manufacturer's instructions, and then used for PCR. For assessment of HHV-6 and HHV-7 DNA levels in peripheral blood, real-time PCR was performed as described in a previous report,[15] and results expressed as viral DNA genome equivalents per 1 mL of whole blood. In DIHS/DRESS, HHV-6 DNA is usually detected during days 14–21 after the onset of skin eruption, whereas it is usually increased in accordance with the skin eruption in GVHD, as described previously.[9]

Immunohistochemistry

Tissues were fixed in formalin, embedded in paraffin wax, and cut into sections 4 μm thick. Immunostaining was performed using anti-CD3 (code A0452; Dako, Glostrup, Denmark) polyclonal antibody, anti-FoxP3 (clone 236 A/E7; BD Biosciences Inc., San Jose, CA, USA), and anti-CD4 (NCL-CD4-368, clone 4B12), anti-CD8 (NCL-C8-295, clone 1A5) (both Novocastra Ltd, Newcastle upon Tyne, UK) monoclonal antibodies as primary antibodies. Biotinylated antimouse IgG was used as secondary antibody, and bound antibody was evaluated using streptavidin-biotinylated peroxidase complex. After washing, sections were exposed to the chromogen and counterstained with haematoxylin. The numbers of immunostained cells in the dermis were counted in five high-power fields (HPF) and expressed as the mean number. The ratios of FoxP3+ Tregs, CD4+ T cells, and the ratio of CD8+ T cells to CD3+ T cells in the dermis were then calculated.

Statistical analysis

Results are expressed as mean ± SEM. Statistical analysis was performed using the Student *t*-test. Pearson correlation coefficient was used to evaluate the correlation between the FoxP3+ Treg/CD3+ T-cell ratio in lesional skin and the number of days from onset. $P < 0.05$ was considered statistically significant.