			福井次矢 (編) 医学書院		
16	橋爪秀夫	Sezary 症候群.	皮膚臨床アセット・皮膚のリンパ腫 古江増隆 岩月啓氏 (編) 中山書店	116-119	2012
17	橋爪秀夫	薬疹・中毒疹.	皮膚疾患トップ 20 攻略本. 古川福実 (編) 南江堂	187-196	2013

永尾圭介

＊印のあるものに関しては巻末に別刷りあり。

	発表者	論文タイトル	発表誌	巻号	ページ	出版年
1＊	永尾圭介	薬疹の検査法—薬剤添加リンパ球刺激試験（DLST）の原理と読み方—.	MB Derma	198	29-34	2012

阿部理一郎

＊印のあるものに関しては巻末に別刷りあり。

	発表者	論文タイトル	発表誌	巻号	ページ	出版年
1＊	Fujita Y Inokuma D Abe R Sasaki M Nakamura H Shimizu T Shimizu H	Conversion from human haematopoietic stem cells to keratinocytes requires keratinocyte secretory factors.	Clin Exp Dermatol	37	658-664	2012
2＊	Saito N Abe R Yoshioka N Murata J Fujita Y Shimizu H	Prolonged elevation of serum granulysin in drug-induced hypersensitivity syndrome.	Brit J Dermatol	167	452-453	2013
3＊	Shinkuma S Inoue A Aoki J Nishie W Natsuga K Ujiie H Nomura T Abe R Akiyama M Shimizu H	The β9 loop domain of PA-PLA1α has a crucial role in autosomal recessive woolly hair/hypotrichosis.	J Invest Dermatol	132	2093-2095	2012
4＊	Nomura Y Nomura T Sakai K Sasaki K Ohguchi Y Mizuno O Hata H Aoyagi S Abe R Itaya Y	A novel splice site mutation in NCSTN underlies a Japanese family with hidradenitis suppurativa.	Br J Dermatol	168	206-209	2013

	Akiyama M Shimizu H					
5	Qiao H Abe R Saito N Fujita Y Hayashi-Ujiie I Wang G Haga S Wu C Ohmiya Y Ozaki M Shimizu H	A method for intravital monitoring of human cells using a far-red luminescent probe in graft-versus-host disease model mice.	J Invest Dermatol	133	841-843	2013
6*	Saito N Yoshioka N Abe R Qiao H Fujita Y Hoshina D Suto A Kase S Kitaichi N Ozaki M Shimizu H	Stevens-Johnson syndrome/toxic epidermal necrolysis mouse model generated by using PBMCs and the skin of patients.	J Allergy Clin Immunol	131	434-441	2013
7	Hoshina D Abe R Yoshioka N Saito N Hata H Fujita Y Aoyagi S Shimizu H	Role of VEGF signaling in angiosarcoma: newly established experimental model and VEGF-targeting therapeutic experiment.				in press

外園千恵

＊印のあるものに関しては巻末に別刷りあり。

	発表者	論文タイトル	発表誌	巻号	ページ	出版年
1＊	中路進之助 上田真由美 外園千恵 稲富勉 木下茂	眼合併症を伴う日本人Stevens-Johnson 症候群のHLA classI 解析.	日本眼科学会雑誌	116 (6)	581-587	2012
2＊	日野智之 外園千恵 稲富勉 福岡秀記 中村隆宏 永田真帆 小泉範子 森和彦 横井則彦 木下茂	羊膜移植の適応と効果.	日眼会誌	116 (4)	374-378	2012
3＊	Ueta M Tokunaga K Sotozono C Sawai H Tamiya G Inatomi T Kinoshita S	HLA-A*0206 with TLR3 Polymorphisms Exerts More than Additive Effects in Stevens-Johnson Syndrome with Severe Ocular Surface Complications.	PLoS One.	7 (8)	e43650	2012
4＊	Ueta M Sotozono C Yamada K Yokoi N Inatomi T Kinoshita S	Expression of prostaglandin E receptor subtype EP4 in conjunctival epithelium of patients with ocular surface disorders: case-control study.	BMJ Open.	2 (5)		2012 Oct 11
5＊	Ueta M Matsuoka T Sotozono C Kinoshita S	Prostaglandin E2 Suppresses Poly I: C-Stimulated Cytokine Production Via EP2 and EP3 in Immortalized Human Corneal Epithelial Cells.	Cornea.	31 (11)	1294-1298	2012

6＊	Ueta M Tamiya G Tokunaga K Sotozono C Ueki M Sawai H Inatomi T Matsuoka T Akira S Narumiya S Tashiro K Kinoshita S	Epistatic interaction between Toll-like receptor 3 (TLR3) and prostaglandin E receptor 3 (PTGER3) genes.	J Allergy Clin Immunol.	129 (5)	1413-1416.e11	2012
7＊	Ueta M Sotozono C Yokoi N Kinoshita S	Downregulation of monocyte chemoattractant protein 1 expression by prostaglandin e2 in human ocular surface epithelium.	Arch Ophthalmol.	130 (2)	249-251	2012
8＊	Kaido M Yamada M Sotozono C Kinoshita S 他 5 名	The relation between visual performance and clinical ocular manifestations in stevens-johnson syndrome.	Am J Ophthalmol.	154 (3)	499-511	2012
9＊	Tohkin M Kaniwa N Saito Y Sugiyama E Kurose K Nishikawa J Hasegawa R Aihara M Matsunaga K Abe M Furuya H Takahashi Y Ikeda H Muramatsu M	A whole-genome association study of major determinants for allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients.	Pharmacogenomics J.	13 (1)	60-69	2013

	Ueta M Sotozono C Kinoshita S Ikezawa Z					
10＊	Sotozono C Inatomi T Nakamura T Koizumi N Yokoi N Ueta M Matsuyama K Miyakoda K Kaneda H Fukushima M Kinoshita S	Visual Improvement following Cultivated Oral Mucosal Epithelial Transplantation.	Ophthalmol	120 (1)	193-200	2013
11＊	外園千恵	総論 眼科・皮膚科の境界領域となる疾患とともに診るべき疾患.	Visual Dermatology	12 (2)	110-112	2013
12＊	上田真由美 外園千恵	Stevens-Johnson 症候群の眼障害.	Visual Dermatology	12 (2)	172-174	2013

[VI]

研究成果の刊行物・印刷

ORIGINAL ARTICLE

Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution

Yukiko Ushigome, MD, Yoko Kano, MD, PhD, Tadashi Ishida, MD, Kazuhisa Hirahara, MD, and Tetsuo Shiohara, MD, PhD
Tokyo, Japan

Background: Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe systemic hypersensitivity reaction caused by specific drugs, in which herpesvirus reactivations and organ dysfunction occur during the course of the disease. Although recent reports have documented the development of autoimmune disease after complete resolution of DIHS/DRESS, relatively little is known about long-term outcomes after complete resolution of the disease.

Objective: The aim of this study was to retrospectively analyze complications and sequelae in the early and late phases of DIHS/DRESS according to treatment.

Methods: In all, 34 patients were classified into 2 groups: 14 patients with oral corticosteroid treatment; and 20 with noncorticosteroid treatment. The disease time course was divided into 2 periods: the first 6 months after onset of the drug reaction (early phase); and the period thereafter (late phase). Investigations to detect the presence of viral/bacterial infectious diseases, organ dysfunction, and autoantibodies were performed in both early and late phases.

Results: Herpesvirus infections and pneumonia were detected in 6 and 2 patients, respectively, in the corticosteroid treatment group in the early phase. In the noncorticosteroid treatment group, 2 patients developed autoimmune diseases, namely lupus erythematosus and autoimmune thyroiditis. Autoantibodies were detected in 44.4% of patients examined in the late phase of the disease.

Limitations: This study only evaluated a small number of autoantibodies.

Conclusion: The need for anti-inflammatory effects from systemic corticosteroids should be balanced with the risk of infectious diseases and the benefits of preventing the appearance of later autoimmune conditions in patients with DIHS/DRESS. (J Am Acad Dermatol 10.1016/j.jaad.2012.10.017.)

Key words: complication; corticosteroid; drug-induced hypersensitivity syndrome; drug reaction; drug reaction with eosinophilia and systemic symptoms; herpesvirus; outcome; treatment; viral reactivation.

Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe systemic hypersensitivity reaction caused by specific drugs such as anticonvulsants and allopurinol, and is characterized by organ dysfunction and reactivation of human herpesvirus (HHV)-6.[1-3] Reactivation of other herpesvirus, such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV) may occur during the course of this drug reaction.[4-6] Despite the complete recovery from DIHS/DRESS, the development of autoimmune sequelae such as autoimmune

From the Department of Dermatology, Kyorin University School of Medicine.
Supported by Research on Measures for Intractable Diseases Project: matching fund subsidy from the Ministry of Health, Labor, and Welfare and by the Ministry of Education, Culture, Sports, Science, and Technology.
Conflicts of interest: None declared.
Accepted for publication October 6, 2012.

Reprint requests: Yoko Kano, MD, PhD, Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa Mitaka, Tokyo 181-8611, Japan. E-mail: kano@ks.kyorin-u.ac.jp.
Published online •••.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2012.10.017

thyroiditis, sclerodermoid lesions, type 1 diabetes mellitus, and lupus erythematosus has been reported.[7-12] The long-term outcomes of DIHS/DRESS after complete resolution of the disease are unclear, because of a lack of long-term follow-up and the potential development of sequelae after a disease-free period of several months to years. In particular, the relationship between administration of systemic corticosteroids—a common treatment for DIHS/DRESS—and long-term outcome is not well documented.[13,14] Long-term outcomes may be influenced by the type and duration of treatment, herpesvirus reactivation, genetic factors, and the presence of underlying disease. To clarify the relationship between treatment and outcome in DIHS/DRESS, we retrospectively analyzed the complications and sequelae in the early and late phases of the disease in relation to treatments in patients with DIHS/DRESS seen at our institution. This study revealed significant differences in outcomes according to treatment for DIHS/DRESS.

CAPSULE SUMMARY

- Drug-induced hypersensitivity syndrome is a severe systemic hypersensitivity reaction, and involves the reactivation of herpesviruses. Various infections and organ failure can develop during the course of this disease.
- Development of autoimmune diseases and autoantibodies were detected in noncorticosteroid-treated patients after complete resolution of the disease.
- Treatments for drug-induced hypersensitivity syndrome should be carefully selected based on an understanding of the differences in treatment modalities.

METHODS

Patients

This study was approved by the institutional review board of Kyorin University School of Medicine, Tokyo, Japan. The medical records of 40 patients who had been admitted into our hospital for DIHS/DRESS between 1998 and 2010 were reviewed. All patients satisfied the diagnostic criteria for DIHS/DRESS proposed by the Japanese Severe Cutaneous Adverse Reaction Group,[15] and the culprit drug had been discontinued once the diagnosis was suspected. Patients were excluded from further analysis if: they were older than 85 years; ~~significant underlying diseases were present, including heart or renal failure; treatment had been initiated prior presentation at our hospital that was unclear~~; or if the period of observation and follow-up was less than 1 year after the initiation of treatment in our hospital. After the exclusion of ineligible patients based on the exclusion criteria, 34 of the 40 patients given the diagnosis of DIHS/DRESS were enrolled in the study. Using the RegiSCAR scoring system proposed by Kardaun et al,[16] the 34 cases were classified as either definite or probable.

Patients were classified into 2 groups according to whether they had been treated with oral corticosteroids (corticosteroids, n = 14; noncorticosteroid treatment, n = 20). No other immunosuppressive agents had been administered. The initial oral corticosteroid dose was 0.6 to 1.0 mg/kg daily, after which the dose was gradually tapered. Most patients required more than 8 weeks of oral corticosteroids to achieve complete resolution. Patients who had received less than 0.25 mg/kg daily within 3 days before hospital admission were not included in the oral corticosteroid treatment group. A total of 5 patients in the corticosteroid treatment group had also received intravenous immunoglobulin (IVIG) therapy, with a dose of 5 g daily administered for 3 to 5 days on detection of herpesvirus reactivation. In the noncorticosteroid treatment group, 3 patients had received IVIG therapy with intravenous fluids. Two patients were given doses of 5 g daily for 3 and 5 days, respectively, and 1 patient who had 1 kidney because of previous excision of a renal tumor was given a dose of 2.5 g daily for 3 days. The other 17 patients were given supportive treatment with intravenous fluids (Fig 1). Some patients ~~had~~ received topical corticosteroids for symptomatic relief. The type of treatment selected was based on the clinical judgment of the consulting dermatologist rather than a predetermined treatment algorithm.

The clinical features and culprit drugs in each group are shown in Table I. The respective mean age was 54.5 ± 19.7 and 56.4 ± 15.2 years in the corticosteroid and noncorticosteroid treatment groups. The type of culprit drugs and the presence of underlying disease were not significantly different between the 2 groups. In most patients, eruptions started as erythematous macules that enlarged and became confluent erythematous lesions. Mucosal lesions were present only in 1 patient in the corticosteroid treatment group. Skin biopsy specimens had been obtained from all patients and histopathological examination revealed scattered exocytosis of mononuclear cells in the epidermis and perivascular lymphocytic and eosinophilic infiltration in the papillary dermis in many specimens. Laboratory data

Abbreviations used:

ATGA: antithyroglobulin antibody
ATPOA: antithyroperoxidase antibody
CMV: cytomegalovirus
DIHS: drug-induced hypersensitivity syndrome
DRESS: drug reaction with eosinophilia and systemic symptoms
EBV: Epstein-Barr virus
HHV: human herpesvirus
IVIG: intravenous immunoglobulin

including leukocyte and eosinophil counts, C-reactive protein, alanine aminotransferase, and serum IgG levels in peripheral blood were obtained before treatment and analyzed to exclude differences in disease severity between the 2 groups; no significant differences were observed in any of these parameters between the 2 groups. The culprit drug was confirmed using the lymphocyte transformation test. Positive lymphocyte transformation test results were obtained more than 1 month after the onset of the drug reaction in most patients.

Assessment of clinical courses

The disease time course was divided into 2 periods: the first 6 months after the onset of a drug reaction was regarded as the early phase and the period thereafter was regarded as the late phase. The average time period of clinical observation (from disease onset until end of follow-up) was 53 and 41 months in the oral corticosteroid and noncorticosteroid treatment groups, respectively. Investigations to detect the presence of viral/bacterial infections and organ dysfunction attributable to DIHS/DRESS were performed in both the early and late phases. Mild liver dysfunction and/or erythematous rash commonly observed during the course of the disease were not considered to be complications of DIHS/DRESS.

Detection of viral reactivation

To detect HHV-6 reactivation, patients with suspected DIHS/DRESS were tested for anti-HHV-6 IgG antibody titers by fluorescent antibody assays and/or real-time polymerase chain reaction assays for HHV-6 DNA loads in peripheral leukocytes, based on *Taq*Man technology. HHV-6 reactivation was defined as a greater than 4-fold increase in anti-HHV-6 IgG antibody titers or detection of HHV-6 DNA in leukocytes. In addition, EBV and CMV DNA loads in peripheral leukocytes were also determined by means of polymerase chain reaction assays, based on *Taq*Man technology, during the course of the disease. DNA loads for herpesvirus were evaluated at either biweekly or triweekly intervals.

Detection of antibody

The presence of autoantibodies and increases in autoantibody levels were also evaluated in both phases. In some patients, serum was obtained before treatment and preserved at −80°C for measurement of autoantibodies including antinuclear antibody, antithyroglobulin antibody (ATGA), and antithyroperoxidase antibody (ATPOA), using a fluorescein-labeled antibody for determination of antinuclear antibody levels and radioimmunoassay for measurement of ATGA and ATPOA levels. The aforementioned antibodies were selected based on preliminary results that had shown no alterations in the levels of rheumatoid factor, antitopoisomerase 1, or antimitochondrial or antithyroglobulin receptor antibodies in patients' sera. Autoantibody levels were measured at intervals of several months in the majority of patients. Autoantibody levels were compared with those before the initiation of treatment.

Statistical analyses

Laboratory data from the 2 treatment groups were analyzed using Student *t* test. Values of *P* less than .05 were taken to indicate statistical significance.

RESULTS

The overall mortality was 8.8%. In the corticosteroid treatment group, various infections such as herpes labialis, herpes zoster, CMV diseases, and pneumonia were seen in the early phase. Herpes labialis was detected within 10 days after the onset of DIHS/DRESS. Herpes zoster occurred in 2 patients approximately 2 months after the onset of drug eruptions during corticosteroid tapering, and 1 month after the cessation of corticosteroid therapy in 1 patient. The cutaneous manifestations of herpes zoster were mild and resolved without any complications.[17] CMV diseases were noted in 1 patient, which manifested as gastrointestinal bleeding and skin ulcers on the back 5 weeks after the onset of DIHS/DRESS,[18] followed by acute respiratory distress syndrome, resulting in death. Limbic encephalitis, possibly associated with HHV-6 reactivation, occurred 3 weeks after the onset of DIHS/DRESS in 1 patient, and was complicated by syndrome of inappropriate secretion of antidiuretic hormone.[19] Some of the cases mentioned in the current study have already been published.[7,8,17-19] Most viral infections, including herpes zoster, encephalitis, and gastrointestinal bleeding, were detected when the dose of oral corticosteroid was decreased to 25% to 67% of the initial dose. In addition, 2 cases of

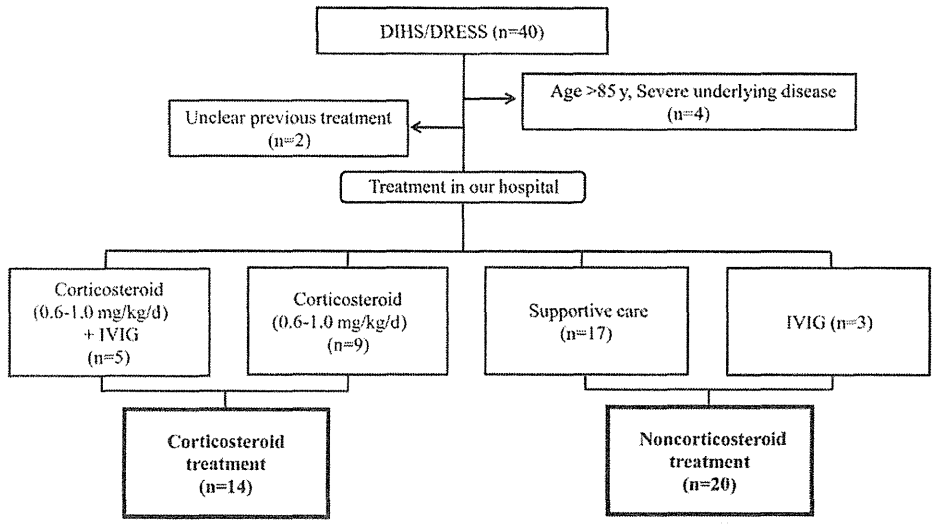

Fig 1. Patient flow diagram. Patients with drug-induced hypersensitivity syndrome (*DIHS*)/drug reaction with eosinophilia and systemic symptoms (*DRESS*) were divided into 2 groups. Administration of intravenous immunoglobulin (*IVIG*) was included in each group. Q7

Table I. Patient characteristics

Treatment group (No. of cases)	Age, y, mean ± SD	M:F	Underlying disease (No. of cases)	Culprit drug (No. of cases)
Corticosteroid (14)	54.5 ± 19.7	10:4	Arrhythmia (1), cerebral infarction (2), colitis (1), convulsion (1), epilepsy (3), hyperuricemia (1), neuralgia (1), psychiatric disease (2), rheumatoid arthritis (1), vasculitis (1)	Allopurinol (1), carbamazepine (6), dapsone (1), mexiletine (1), phenobarbital (2), phenytoin (1), salazosulfapyridine (2)
Noncorticosteroid (20)	56.4 ± 15.2	8:12	Cerebral infarction (3), convulsion (5), encephalitis/asthma (1), epilepsy (1), hyperuricemia (1), hyperuricemia/Sjögren syndrome (1), hyperuricemia/hepatitis C/renal tumor (1), neuralgia (4), psychiatric disease (3)	Allopurinol (3), carbamazepine (14), phenobarbital (1), phenytoin (2)

F, Female; *M*, male.

pneumonia occurred: 1 patient died of acute respiratory distress syndrome secondary to *Pneumocystis jiroveci* pneumonia 2.5 months after the onset of DIHS/DRESS; and another patient with interstitial pneumonia developed *Cryptococcus* pneumonia 8 months after the onset of DIHS/DRESS. In these 2 patients, infectious pneumonia was observed when the doses of corticosteroid were reduced to 50% and 15% of the initial dose, respectively. Bacterial intramuscular abscess occurred in 1 patient when the dose was decreased to 75% of the initial dose [T2] (Table II).

In the early phase of DIHS/DRESS in the noncorticosteroid treatment group, diffuse alopecia developed 4 months after the onset of DIHS/DRESS in 1 patient without evidence of thyroid dysfunction, which persisted for 6 months. Another patient with gastrointestinal bleeding caused by CMV infection required emergency endoscopic clipping and administration of ganciclovir with IVIG.[18] In contrast to the corticosteroid treatment group, no bacterial infections were seen in the noncorticosteroid treatment group in the early phase (Fig 2). [F2]

Liver dysfunction was observed in all patients in the early phase. Severe liver dysfunction (alanine aminotransferase >300 IU/L) was detected in 8 patients, and in 4 of these 8 patients the corticosteroid was administered at the initial dose of 0.8 mg/kg daily. The others were managed with supportive treatment monitored by specialists. Liver dysfunction

Table II. Onset of complications and corticosteroid treatment doses

Case No.	Age, y/gender	Underlying disease	Culprit drug	Complication after treatment	Corticosteroid (prednisolone)	
					Initial dose, mg/d	Dose at onset of complication, mg/d
1	39/M	Psychiatric disease	Carbamazepine	HZ	40	10
2	63/M	Convulsion	Carbamazepine	HZ	40	20
3	70/F	Cerebral infarction	Phenytoin	HZ	40	0
4	69/M	Epilepsy	Phenobarbital	En	60	40
5	74/M	Arrhythmia	Mexiletine	GB → ARDS	50	25 → 20
6	79/M	Neuralgia	Carbamazepine	AC → PP → ARDS	50	40 → 25 → 25
7	28/F	Epilepsy	Carbamazepine	IA	80	60
8	68/M	Rheumatoid arthritis	Salazosulfapyridine	IP → CP	40	15 → 6*

AC, Acute cholangitis; *ARDS*, acute respiratory distress syndrome; *CP*, *Cryptococcus* pneumonia; *En*, encephalitis; *F*, female; *GB*, gastrointestinal bleeding; *HZ*, herpes zoster; *IA*, intramuscular abscess; *IP*, interstitial pneumonia; *M*, male; *PP*, *Pneumocystis jiroveci* pneumonia.
*Administration of corticosteroids continued because of rheumatoid arthritis.

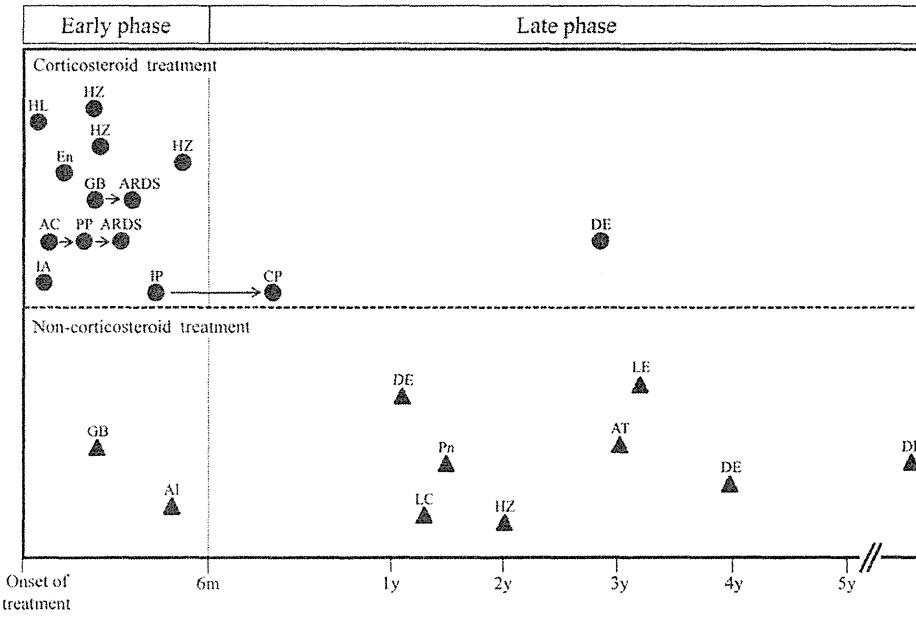

Fig 2. Complications and sequelae were classified into 2 groups in early and late phases according to treatment. *AC*, Acute cholangitis; *Al*, alopecia; *ARDS*, acute respiratory distress syndrome; *AT*, autoimmune thyroiditis; *CP*, *Cryptococcus* pneumonia; *DE*, drug eruption; *En*, encephalitis; *GB*, gastrointestinal bleeding; *HL*, herpes labialis; *HZ*, herpes zoster; *IA*, intramuscular abscess; *IP*, interstitial pneumonia; *LC*, lung cancer; *LE*, lupus erythematosus; *Pn*, pneumonia; *PP*, *Pneumocystis jiroveci* pneumonia.

ameliorated within 80 days in most patients, with some fluctuations in the levels. No fatal sequelae were noted in the current study.

In the late phase of DIHS/DRESS in the non-corticosteroid treatment group, autoimmune diseases developed in some patients. Lupus erythematosus with severe lupus nephritis developed in a patient 4 years after the onset of DIHS/DRESS treated with IVIG alone.[8] A case of asymptomatic autoimmune thyroiditis (Hashimoto thyroiditis) developed in a patient 3 years after the onset of DIHS/DRESS managed with supportive treatment alone. In this patient, thyroid stimulation hormone level increased 10 months after the onset of DIHS/DRESS, followed by detection of ATGA and ATPOA. One patient with a normal x-ray result on admission died of lung cancer 2 years after the onset of DIHS/DRESS. Drug eruptions were seen in 3 patients, caused by an antibiotic, an antilipemic agent, and a cold remedy, respectively (Fig 2). The

Table III. Detection of autoantibodies

	Detection of autoantibody	
	Frequency Detected antibodies (No. of cases)	
Treatment group (No. of cases)	Early phase	Late phase
Corticosteroid (6)	0% (0/6)	16.7% (1/6) ANA (1)
Noncorticosteroid (10)	20.0% (2/10) ANA (2)	70.0% (7/10) ANA (2) ATGA (4) ATPOA(3)

ANA, Antinuclear antibody; *ATGA*, antithyroglobulin antibody; *ATPOA*, antithyroperoxidase antibody.

Table IV. Herpesvirus reactivations

	Viral reactivation, no. of cases			
Treatment group (No. of cases)	HHV-6, EBV, CMV	HHV-6, EBV	HHV-6, CMV	HHV-6
Corticosteroid (13)	3	2	4	4
Noncorticosteroid (16)	2	7	1	6

CMV, Cytomegalovirus; *EBV*, Epstein-Barr virus; *HHV*, human herpesvirus.

lymphocyte transformation test levels were positive in 2 of these 3 cases.

Autoantibodies were more commonly detected in patients in the noncorticosteroid treatment group, particularly in the late phase, with 44.4% of patients demonstrating autoantibodies. One patient with positive ATPOA in the corticosteroid treatment group had a history of rheumatoid arthritis. Autoantibodies were present in all 3 patients who had been treated with IVIG alone (Table III). The respective ranges for antinuclear antibody, ATGA, and ATPOA detected were ~~40 to 320×~~, 1.5 to 8.1 U/L, and 1.0 to 19.5 U/L. These autoantibody titers remained elevated during the study period, with some fluctuations in the levels.

Herpesvirus reactivations detected during the course of the disease were classified into 4 groups: HHV-6, EBV, and CMV; HHV-6 and EBV; HHV-6 and CMV; and HHV-6 alone. Our results showed that CMV reactivation was detected more than half of the patients in the corticosteroid treatment group. EBV reactivation was more frequently observed in patients in the noncorticosteroid treatment group than in the corticosteroid treatment group (Table IV).

DISCUSSION

Little attention has been paid to the long-term outcomes after complete recovery from DIHS/DRESS because many difficulties are encountered in following up with patients who do not seek medical care during a disease-free period after clinical resolution. This study revealed long-term outcomes obtained from a substantial number of patients with DIHS/DRESS who were carefully followed up by the same dermatologists in a single institution.

The prognosis of DIHS/DRESS may be influenced by age, genetic factors, presence of underlying disease, viral reactivation, and type of treatment. In particular, DIHS/DRESS appears to be worse in elderly patients, whereas younger patients recover more quickly. In the current study, ~~the 2 treatment groups were age-matched and laboratory data obtained before the initiation of therapy showed no significant differences between the 2 groups~~; thus, patient selection bias was unlikely.

Oral corticosteroids remain the mainstay treatment for DIHS/DRESS,[13,14] and a rapid resolution of symptoms is usually observed within several weeks after commencement. In this study, various infections were noted in the corticosteroid treatment group in the early phase, including herpesvirus diseases and *P jiroveci* pneumonia. CMV reactivation was more commonly detected in the corticosteroid treatment group, occurring in 53.8% examined. CMV disease and *P jiroveci* pneumonia were associated with delayed recovery and worse outcomes. Based on our results, most infectious diseases appeared within 3 months after initiation of the oral corticosteroid. As a result, careful follow-up for at least 3 months is recommended to minimize the risk of unfavorable outcomes in patients with DIHS/DRESS. The prolonged administration of oral corticosteroids may be partly responsible for these infections, given that the corticosteroid dose at 0.8 to 1.0 mg/kg daily was relatively high and administered over a long period, with the corticosteroid tapered over 2 months. However, considering the relatively high doses of corticosteroid used to treat other diseases such as collagen diseases and systemic vasculitis, it seems unlikely that corticosteroid alone was responsible for the infections in patients with DIHS/DRESS. In fact, 1 patient with gastrointestinal bleeding and skin ulcers caused by CMV disease had not been treated with oral corticosteroids.[18]

Alternatively, the development of infections in DIHS/DRESS during corticosteroid treatment may be analogous to the pathomechanisms of immune reconstitution inflammatory syndrome.[20] Diseases in the early stage of DIHS/DRESS such as herpes zoster, CMV infection, and *P jiroveci* pneumonia are similar to the range of illnesses in patients with AIDS and immune reconstitution inflammatory syndrome after highly active antiretroviral therapy.[21] As infectious

diseases occurred most commonly during corticosteroid tapering down to 25%, the dose reduction of corticosteroids in the setting of DIHS/DRESS might have contributed to the appearance of these infectious diseases. An awareness of these infectious diseases during tapering will facilitate prompt interventions in patients with DIHS/DRESS.

The development of autoimmune diseases such as lupus erythematosus[8] and autoimmune thyroiditis, along with the presence of autoantibodies, were observed in the noncorticosteroid treatment group in the late phase of DIHS/DRESS. Our previous article reported a patient who developed sclerodermoid graft-versus-host disease–like lesions treated with oral corticosteroids and low-dose IVIG in another hospital.[7] However, surprisingly, no cases of autoimmune disease were seen in the corticosteroid treatment group in the current study, and the appearance of autoantibodies was uncommon. It has been shown that IVIG compensates for the decreased immunoglobulin concentration, provides anti-inflammatory effects, and regulates the immune response in autoimmune diseases. However, according to Joly et al,[22] IVIG in patients with DIHS/DRESS can result in severe adverse events, which may require systemic corticosteroid therapy. In the current study, autoantibodies were detected in all 3 patients treated with IVIG. As only a small number of patients were enrolled in this study, it is difficult to determine the role of IVIG in the management of DIHS/DRESS. Further studies on treatment outcomes and long-term follow-up are thus needed in a larger patient population. Clearly, further work needs to be done regarding the link between the onset of DIHS/DRESS and the occurrence of cancer.

It is unclear why autoimmune diseases develop in the noncorticosteroid treatment group in DIHS/DRESS. We have already reported that regulatory T cells were expanded in the acute stage with normal functions, whereas regulatory T cells were functionally impaired in the resolution stage in patients with DIHS/DRESS.[23] These regulatory T cells most likely increased the susceptibility of patients with DIHS/DRESS to autoimmune diseases. However, autoimmune reactions could not be detected in all patients with DIHS/DRESS. Impaired regulatory T-cell function might thus contribute partially to the development of autoimmune diseases, but other pathomechanisms might also be responsible for the appearance of autoimmune reactions. On the other hand, we speculate that this may be linked to the EBV reactivation, because EBV shows a unique characteristic infection pattern of B cells. EBV infection might be a continuous source of chronic immune stimulation.[24] In fact, EBV has been implicated in the development of autoimmune diseases, such as lupus erythematosus and multiple sclerosis.[25,26] In the current study, EBV reactivation was more frequently detected in patients in the noncorticosteroid treatment group, with 56.3% of patients examined. This frequency was much higher than that in patients in the corticosteroid treatment group. In this regard, we have detected that viral loads of EBV are lower in the corticosteroid treatment group than in the noncorticosteroid treatment group, whereas viral loads of HHV-6 and CMV are higher in the corticosteroid treatment group than in the noncorticosteroid group (in preparation by Ishida). These findings may indicate that the pattern of viral reactivations enhanced by systemic corticosteroids would differ according to the virus.

Although only limited information could be obtained concerning the detection of autoantibodies, the frequency of the detection for autoimmune thyroid antibodies was markedly higher in the noncorticosteroid treatment group than in the corticosteroid treatment group. Considering that EBV antigens were found in target organs in multiple sclerosis,[27] the thyroid gland might be one of the target organs in this setting.

Our findings suggest that patients with DIHS/DRESS should be monitored for the development of autoimmune disease including laboratory examination of autoantibodies, despite clinical symptoms. The beneficial effects of oral corticosteroids in the suppression of inflammation and prevention of autoimmune disease need to be counterbalanced against the risk of infection.

REFERENCES

1. Descamps V, Bouscarat F, Laglenne S, Aslangul E, Veber B, Descamps D, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive hemophagocytic syndrome. Br J Dermatol 1997;137:605-8.
2. Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T. Human herpesvirus 6 infection as a risk factor for the development of severe drug-induced hypersensitivity syndrome. Arch Dermatol 1998;134:1108-12.
3. Tohyama M, Yahata Y, Yasukawa M, Inagi R, Urano Y, Yamanishi K, et al. Severe hypersensitivity syndrome due to sulfasalazine associated with reactivation of human herpesvirus 6. Arch Dermatol 1998;134:1113-7.
4. Kano Y, Hirahara K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. Br J Dermatol 2006;155:301-6.
5. Seishima M, Yamanaka S, Fujisawa T, et al. Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug-induced hypersensitivity syndrome. Br J Dermatol 2006;115:344-9. Q6
6. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transl Med 2010;2:45ra62.

7. Kano Y, Sakuma K, Shiohara T. Sclerodermoid graft-versus-host disease—like lesions occurring after drug-induced hypersensitivity syndrome. Br J Dermatol 2007;156:1061-3.
8. Aota N, Hirahara K, Kano Y, Fukuoka T, Shiohara T. Systemic lupus erythematosus presenting with Kikuchi-Fujimoto's disease as a long-term sequel of drug-induced hypersensitivity syndrome; a possible role of Epstein-Barr virus reactivation. Dermatology 2009;218:275-7.
9. Brown RJ, Rother KI, Artman H, Mercurio MG, Wanq R, Looney RJ, et al. Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. Arch Dermatol 2009;145:63-6.
10. Eshki M, Allanore L, Musette P, Milipied B, Grange A, Guillaume JC, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol 2009;145:67-72.
11. Sekine N, Motokura T, Oki T, et al. Rapid loss of insulin secretion in a patient with fulminant type 1 diabetes mellitus and carbamazepine hypersensitivity syndrome. JAMA 2001;285:1153-4.
12. Chiou CC, Chung WH, Hung SI, Yang LC, Hong HS. Fulminant type 1 diabetes mellitus caused by drug hypersensitivity syndrome with human herpesvirus 6 infection. J Am Acad Dermatol 2006;54(Suppl):S14-7.
13. Chiou CC, Yang LC, Hung SI, Chang YC, Kuo TT, Ho HC, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol 2008;22:1044-9.
14. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med 2011;124:588-97.
15. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol 2007;156:1083-4.
16. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.
17. Kano Y, Horie C, Inaoka M, Ishida T, Shiohara T. Herpes zoster in patients with drug-induced hypersensitivity syndrome/-DRESS. Acta Dermatol Venereol 2012;92:206-7.
18. Asano Y, Kagawa H, Kano Y, Shiohara T. Cytomegalovirus disease during severe drug eruptions: report of 2 cases and retrospective study of 18 patients with drug-induced hypersensitivity syndrome. Arch Dermatol 2009;145:1030-6.
19. Sakuma K, Kano Y, Fukuhara M, Shiohara T. Syndrome of inappropriate secretion of antidiuretic hormone associated with limbic encephalitis in a patient with drug-induced hypersensitivity syndrome. Clin Exp Dermatol 2008;33:287-90.
20. Shiohara T, Kurata M, Mizukawa Y, Kano Y. Recognition of immune reconstitution syndrome necessary for better management of patients with severe drug eruption and those under immunosuppressive therapy. Allergol Int 2010;59:333-43.
21. Leohloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatol Clin 2006;24:549-70.
22. Joly P, Janela B, Tetart F, et al. Poor benefit/risk balance of intravenous immunoglobulins in DRESS. Arch Dermatol 2012;148:543-4.
23. Takahashi R, Kano Y, Yamazaki Y, et al. Defective regulatory T cells in patients with severe drug eruptions: timing of the dysfunction is associated with the pathological phenotype and outcome. J Immunol 2009;182:8071-9.
24. Aota N, Shiohara T. Viral connection between drug rashes and autoimmune diseases: how autoimmune responses are generated after resolution of drug rashes. Autoimmune Rev 2009;8:488-94.
25. Chen MR. Epstein-Barr virus, the immune system, and associated diseases. Front Microbiol 2011;2:5.
26. Niller HH, Wolf H, Ay E, Minarovits J. Epigenetic dysregulation of Epstein Barr virus latency and development of autoimmune disease. Adv Exp Med Biol 2011;711:82-102.
27. Tselis A. Epstein-Barr virus cause of multiple sclerosis. Curr Opin Rheumatol 2012;24:424-8.

皮膚病診療：35(1)；35～38, 2013

◇サルコイドーシス――2013<臨床例>――④

フェニトインによる薬疹後に帯状疱疹を生じ，サルコイドーシスを続発した例

稲岡　峰幸*　　狩野　葉子**　　塩原　哲夫**

Key words
サルコイドーシス，帯状疱疹，フェニトイン

症例のポイント

・フェニトインによる薬疹を生じた15カ月後にフェニトイン再投与による薬疹が発症し，1カ月後に帯状疱疹が出現，その後，サルコイドーシスを続発した例を経験した．
・水痘-帯状疱疹ウイルス(以下，VZV)は肉芽腫反応を誘発しやすく，帯状疱疹後に肉芽腫を生じた例は多数報告されている．
・自験例では再活性化したVZVがサルコイドーシス発症の誘因となった可能性が示唆された．

症例　74歳，女．

初診　2009年8月．

家族歴　特記すべきことなし．

既往歴　73歳，変形性頸椎症．

現病歴　2009年7月，右肋間帯状疱疹罹患2日後に急性硬膜下血腫を発症し当院脳外科に入院し，フェニトイン内服開始．内服13日目に全身に紅斑が出現し，内服23日目に38℃台の発熱を認めたため，当科受診．薬疹の疑いでフェニトインを中止したが，改善傾向なく25日目に当科に入院した．

現症　顔面にはびまん性に紅斑が認められ，軀幹・四肢では大豆大までの浮腫性紅斑が多発融合していた(**図1**)．右前胸部に小豆大の瘢痕が集簇し，頸部リンパ節は拇指頭大に腫脹していた．

臨床検査成績

第13病日；WBC 6,400/μl(Band 3.0%〈正常値＜0.0〉, Neut 63.0%〈42.0-62.0〉, Eos 16.5%〈1.0-5.0〉, Mono 3.0%, Lym 14.0% (25.0-45.0), BUN 30.4 mg/dl, Cr 2.4mg/dl(0.2-0.8), AST 46 IU/l, ALT 26 IU/l(3-30), γ-GTP 74 IU/l(4-50), LDH 641 IU/l(118-226), CRP 6.3 mg/dl(0.0-0.4), IgG 1,406 mg/dl. 胸部X線では異常所見はみられなかった．第14病日;薬剤リンパ球刺激試験：フェニトイン 147%(180%以上が陽性)，第60病日；フェニトイン 398%.

ウイルス学的検索

第13病日；HHV-6 IgG 10倍(10倍未満陰性)，VZV-IgG 280(＜2.0), HSV-IgG 57.2(＜2.0)，全血中HHV-6 DNA 20copy/10^6WBC未満(20copy/10^6WBC未満 陰性)．第26病日；HHV-6 IgG 10倍, VZV-IgG 169, HSV-IgG 70.3.

病理組織学的所見

腹部の紅斑を，第13病日に生検した．表皮では表皮突起の消失がみられ，真皮上層から深層の血管周囲にリンパ球主体の炎症細胞浸潤が認められた(**図2**)．明らかな肉芽腫の形成はみられなかった．

*Inaoka, Miyuki(科長)　阿伎留医療センター皮膚科(〒197-0834 あきる野市引田78－1)
**Kano, Yoko(教授)／Shiohara, Tetsuo(教授)　杏林大学医学部付属病院皮膚科(〒181-8611 三鷹市新川6－20－2)

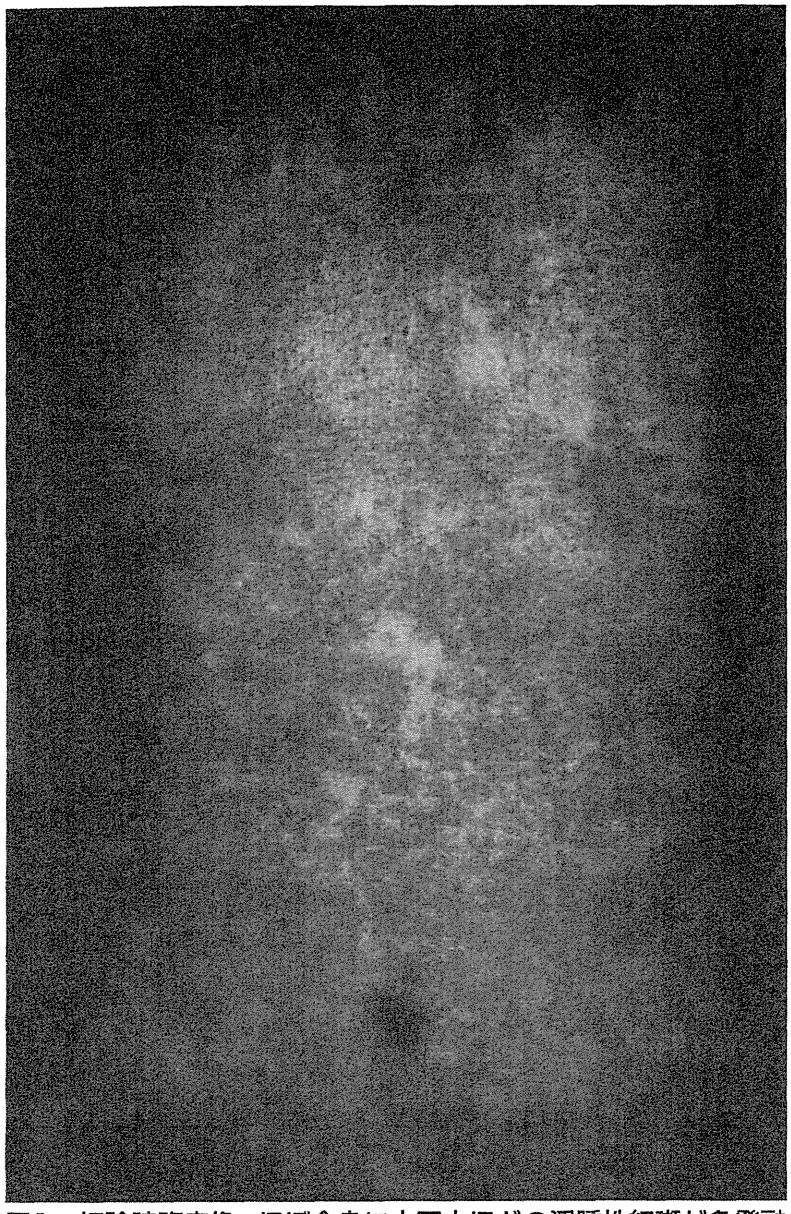

図1　初診時臨床像．ほぼ全身に大豆大ほどの浮腫性紅斑が多発融合していた．

鑑別診断

伝染性単核球症：伝染性単核球症と薬疹は，臨床的に類似し，鑑別が困難な場合が多い．発熱・リンパ節腫脹から始まり，4，5日して全身に小型の紅斑・紫斑が多発する．若年者に多い．自験例では伝染性単核球症に特徴的な扁桃の白苔や高度の肝機能障害は認められなかった．

麻疹：臨床的には高熱，全身性の紅斑が類似する．しかし，自験例では麻疹に特徴的なKoplik斑はみられず，検査所見で好酸球の割合が増加していた．

風疹：発熱は軽微で，顔面を含む全身に粟粒大紅色丘疹・小紅斑が多発する．口腔内に点状出血(Forschheimer斑)を認める．重篤感がなく，紅斑は3日ほどで消褪する．自験例では皮疹・発熱は遷延化した．

診断確定

フェニトイン投与後に，38℃以上の発熱と全身の紅斑を生じ，頸部リンパ節腫脹がみられた．肝障害・腎障害を合併しており，経過中に好酸球の上昇が続きDIHSを強く疑わせた．HHV-6IgG抗体価を検出したが上昇は認められず，DIHSの診断基準を完全に満たさないため，フェニトインによる多形紅斑型薬疹と診断した．

治療と経過

被疑薬であるフェニトインをゾニサミドに変更し，補液のみで加療した．紅斑の再燃がみられたが，その後，発熱・紅斑は徐々に消褪し，第28病日に退院した．退院15カ月後に，他院にて，てんかんを発症し，フェニトインが再投与された．その後全身に紅斑・発熱・肝障害を生じ，約1カ月後に再び右肋間帯状疱疹を発症し，入院となった．帯状疱疹に引き続いて意識レベルの低下，幻視，ぶどう膜炎，左顔面神経麻痺が続発した(図3)．胸部X線およびCTでは肺門部リンパ節腫脹がみられ，ACE 51.6(保存血清を用いて検査した当科入院時のACE 9.1)と高値を呈していた．臨床・検査所見からサルコイドーシスと診断され，プレドニゾロン35 mg/dayによる治療が開始された．その後，意識障害やぶどう膜炎は徐々に改善した．

考　按

自験例は薬剤性過敏症症候群(DIHS)の診断基準を完全には満たさなかったが，原因内服薬，紅

斑の再燃，2回目のDLSTの陽性結果などから，DIHSに極めて類似した病態を呈したフェニトインによる薬疹と捉えられる．われわれは以前に帯状疱疹後に発症したDIHS患者の皮膚生検において，肉芽腫反応がみられた症例を報告し，水痘-帯状疱疹ウイルス(VZV)が，肉芽腫の形成に関与している可能性を報告している[2,3]．

自験例は1回目のフェニトイン投与の薬疹の皮膚生検では肉芽腫反応はみられなかったが，2回目のフェニトイン投与後にサルコイドーシスを発症しており，この時点で皮膚生検を施行していたならば，皮膚における肉芽腫反応がみられた可能性がある．

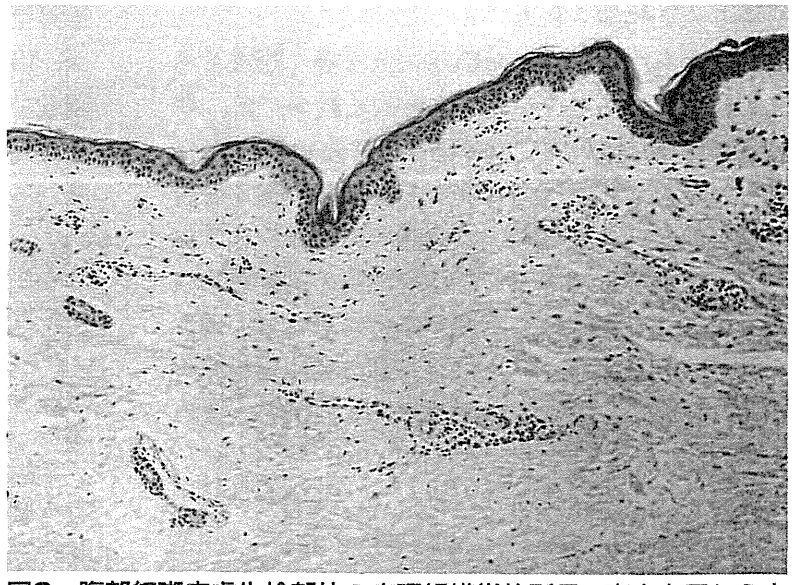

図2　腹部紅斑皮膚生検部位の病理組織学的所見．真皮上層から中層の血管周囲にリンパ球主体の炎症細胞浸潤がみられた(H-E染色，×40)．

肉芽腫を形成する要因としては刺青，抗酸菌や，*Propionibacterium acnes*，VZVなどがあげられている．自験例は原因薬剤が2回投与されているが，いずれの際にも帯状疱疹を同部位に発症している．DIHSで検出されるヘルペスウイルスの再活性化と同様にDIHSに類似した病態を有していた自験例においても原因薬剤の投与後に再活性化したVZVが肉芽腫形成に関与し，サルコイドーシスを

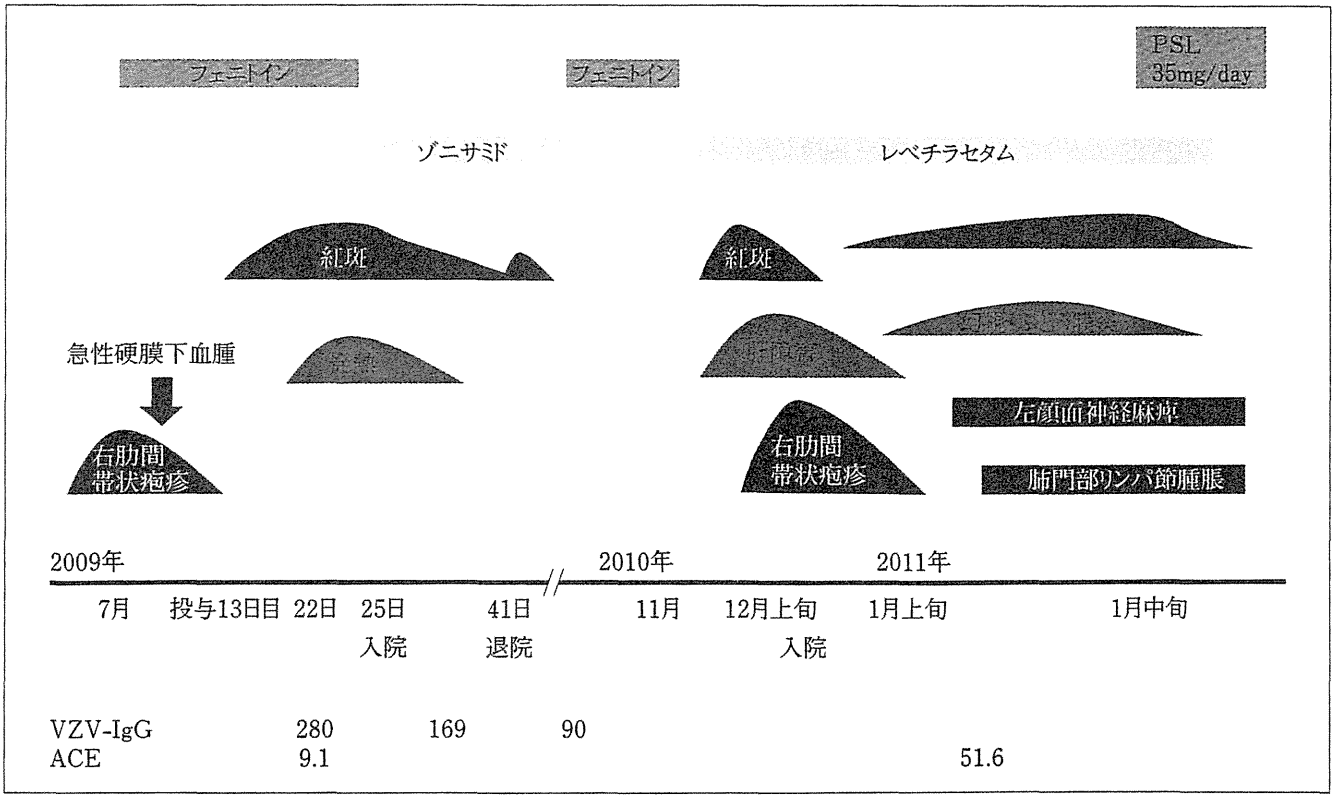

図3　自験例の経過

発症したと推測された．

古くから帯状疱疹の瘢痕部に肉芽腫を形成することはよく知られている．文献的な検索では，帯状疱疹後肉芽腫の報告例は国内外あわせて51例[5~7]あり，51例中13例に白血病などの血液疾患を合併していた．これらの中には血液疾患自体や化学療法による免疫学的変化が帯状疱疹後の肉芽腫形成をもたらした可能性を示唆するものもあり，明確な記載は認められないものの一部は免疫再構築症候群[8]としてとらえることのできる症例も含まれていた．

Gibneyら[7]の組織中のウイルスに関する検討では，肉芽腫中のVZV-DNAをPCR法で測定した3例中2例ではVZV-DNAは検出されなかったが，1例では陽性であった．そこでわれわれは，VZV glycoprotein1(gp1)に対するモノクローナル抗体を用いて皮疹部の免疫組織化学染色を施行した[9]．当教室の堀江らは，帯状疱疹の皮疹部のVZV抗原染色を施行し，エクリン汗腺には発症早期から後期にかけて一貫してVZV抗原が6割以上に認められたこと，さらに，汗腺周囲に炎症細胞浸潤が増加している場合はVZV抗原が検出されにくい傾向があることを報告している[10]．

なお，当教室で皮膚の組織学的検査で肉芽腫を形成しなかった典型DIHS10例の皮疹部のVZV抗原染色を行ったところ，陽性4例，陰性6例であった．VZV抗原の発現はDIHSで普遍的にみられる現象ではなく，肉芽腫形成例に多くみられる所見と考えられるが，今後のさらなる検討が必要である．

本症例は第62回日本皮膚科学会中部支部学術大会で報告した．

至誠会第二病院神経内科，立花綾乃先生，板橋美貴子先生，久保昌史先生，宮崎一秀先生に深謝いたします．

本論文は厚生労働省科学研究費補助金「難治性疾患等克服研究事業(難治性疾患克服研究事業)および文部科学省・日本学術振興会科学研究費補助金の援助を受けた．

<文　献>

1) 福本大輔ほか：日皮会誌　**120**：23, 2010
2) 稲岡峰幸ほか：臨皮　**63**：817, 2009
3) Inaoka, M. et al.：Am J Dermatopathol　**33**：872, 2011
4) Fernando, S.L. et al.：Am J Dermatopathol　**31**：611, 2009
5) 石田恵巳留，戸倉新樹：臨皮　**59**：14, 2005
6) Nikkels, A.F., Piérard, G.E.：Clin Exp Dermatol　**23**：237, 1998
7) Gibney, M.D.et al.：Br J Dermatol　**134**：504, 1996
8) Shiohara, T. et al.：Allergol Int　**55**：1, 2006
9) 堀江千穂ほか：臨皮　**64**：109, 2010
10) Horie, C. et al.：Br J Dermatol　**165**：802, 2011