the anti-IRF-3 antibody overnight at 4°C. After washing with phosphate-buffered saline, the cells were incubated with fluorescein-labeled goat anti-rabbit IgG for 30 minutes at 37°C. 4,6-Diamidino-2-phenylindole staining of the nucleus was also performed. The stained cells were visualized at an original magnification of ×40 under an LSM 510 microscope (Carl Zeiss, Jena, Germany). Images were captured using the LSM 510 software.

RT-PCR

Total RNA samples were isolated using Isogen (Nippon Gene, Tokyo, Japan), and RT-PCR was performed using RT-PCR High Plus (Toyobo, Osaka, Japan) (Dai *et al.*, 2004b). The expression levels of *MIP-1α* and glyceraldehyde-3-phosphate dehydrogenase mRNA were detected using specific primers (primer list: Table S1). The PCR products were sequenced to confirm the accuracy of amplification.

Real-time RT-PCR

Real-time RT-PCR was performed in an ABI PRISM 7700 sequence detector (PE Applied Biosystems, Foster City, CA). The primers and probes for glyceraldehyde-3-phosphate dehydrogenase, *TLR3*, and *IRF-7* were obtained from Applied Biosystems (Norwalk, CT). The primers and probes for members of the human *SOCS* family are shown in Table S2. The RNA analysis was carried out using the TaqMan RT-PCR Master Mix reagents kit (Applied Biosystems, Norwalk, CT) and the quantification of gene expression was performed using the comparative computed tomography method, as described previously (Dai *et al.*, 2004a). The level of target gene expression in the test samples was normalized to the corresponding glyceraldehyde-3-phosphate dehydrogenase level and is reported as the fold difference. In this study, each assay was performed in triplicate, and the factorial change of each sample was normalized against that of the vehicle as one unit.

ELISA

Culture supernatants were collected at the indicated times after treatment and were stored at −70°C until subjected to ELISA. The ELISA kit for MIP-1α was purchased from Endogen (Auburn, MA). ELISA was performed according to the manufacturer's instructions.

Protein preparation and Western blot analysis

The cells were harvested by transfer into extraction buffer that contained 150 mM NaCl, 1% Nonidet P-40, 0.5% deoxycholate, 0.1% SDS, 50 mM Tris-HCl (pH 7.4), and protease inhibitors. Equal amounts of protein were separated by SDS-PAGE electrophoresis and transferred to polyvinylidene difluoride membranes. The analysis was performed using the Vistra ECF kit (Amersham Biosciences, Tokyo, Japan) and a FluorolImager (Molecular Dynamics, Sunnyvale, CA).

Statistical analyses

In this study, at least three independent experiments were performed, with similar results, and one representative experiment is shown in each of the figures. The quantitative ELISA data and the relative mRNA expression levels detected by real-time RT-PCR are expressed as the mean ± SD ($N=3$). Statistical significance was determined by the paired Student's *t*-test. Differences were considered to be statistically significant for $P<0.05$. The levels of statistical significance are indicated as follows in the figures: $*P<0.05$; $**P<0.01$; and $***P<0.001$.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

Table S1. Primer pairs for RT-PCR.

Table S2. Primer and probe list for real time RT-PCR.

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Dramatic improvement of psoriatic erythroderma after acute hepatitis: analysis of cytokine synthesis capability in peripheral blood T cells

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CD8+ T cells, etretinate, hepatitis C virus, interferon-γ, psoriasis

Conflicts of interest
None declared.

Summary

We report a patient with psoriasis and hepatitis C virus infection who initially presented with psoriatic erythroderma and eventually showed complete clearance of psoriatic lesions following acute hepatitis induced by etretinate treatment. Cytokine synthesis capabilities in peripheral blood T cells obtained at different stages were evaluated in this patient. A dramatic increase in the frequency of interferon-γ-producing CD8+ T cells in peripheral blood was observed during the erythrodermic stage. In contrast, the frequencies of interleukin (IL)-4- and IL-13-producing CD4+ T and CD8+ T cells were remarkably high at the resolution stage. These results clearly indicate that a shift towards type 2 cytokine predominance contributes to the resolution of severe psoriasis.

Psoriasis is a chronic inflammatory skin disease characterized by T cell-mediated hyperproliferation of keratinocytes.[1] Although recent studies have shown that type 1 cytokines play an important role in the development of inflammation associated with psoriasis, it remains to be determined whether resolution of inflammation in psoriasis would be associated with a shift in the type 1/type 2 cytokine balance towards a type 2 response.[2–6]

We describe a patient with psoriasis and hepatitis C virus (HCV) infection who initially presented with psoriatic erythroderma and eventually showed complete clearance of psoriatic lesions following acute hepatitis induced by etretinate treatment. Cytokine synthesis capabilities in peripheral blood T cells obtained at different stages, the erythrodermic stage and resolution stage, were evaluated in this patient. Results show that type 1 CD8+ T cells activated by the drug play a role in decreasing the viral load while causing the immunopathology, such as deterioration of psoriatic erythroderma and hepatitis, and indicate that a shift from a type 1 to a type 2 response could contribute to the resolution of psoriasis.

Case report

A 47-year-old man presented with a 10-year history of scaly erythematous patches. Although he had been treated with betamethasone valerate ointment (5–10 g daily) and small amounts of oral corticosteroids (2·5 mg daily), he developed psoriatic erythroderma, probably associated with his intermittent use of topical corticosteroids. He had been diagnosed as having HCV infection (without cirrhosis) because of a blood transfusion after a serious trauma when he was 38 years old. After complete withdrawal of the topical corticosteroids, his skin lesions deteriorated with a high-grade fever (Fig. 1a). A biopsy of a plaque on his arm revealed the histological features of psoriasis. Laboratory studies gave the following values: white blood cell count $13{\cdot}2 \times 10^9\ L^{-1}$; platelets $255 \times 10^9\ L^{-1}$; aspartate aminotransferase (AST) 51 IU L^{-1}; alanine aminotransferase (ALT) 36 IU L^{-1}; lactate dehydrogenase (LDH) 415 IU L^{-1}. The level of HCV RNA was 2300 genome equivalents mL^{-1}. Because of no improvement of the psoriatic lesions with topical vitamin D_3 applications, approximately 2 weeks after the development of psoriatic erythroderma treatment with etretinate 40 mg daily was initiated without any topical treatment other than emollients. Twelve days after he started etretinate administration, the patient developed fulminant hepatitis: AST 723 IU L^{-1}; ALT 308 IU L^{-1}; LDH 693 IU L^{-1}. Other hepatitis screening tests were negative, including tests for hepatitis B (HB)s antigen, anti-HBs and antihepatitis A virus antibodies. The enzyme immunoassay IgM titre to cytomegalovirus was 0·32 (positive >0·80), and of viral capsid antigen IgM to Epstein–Barr virus was less than 10-fold (positive >10-fold). Ultrasonography showed no hepatic abnormality. The administration of etretinate was discontinued immediately. Three weeks after the cessation of etretinate, the liver dysfunction returned to normal. Interestingly, the development of drug-induced hepatitis was associated with a rapid decline in serum HCV load, which fell to 98 genome equivalents mL^{-1} during etretinate therapy.

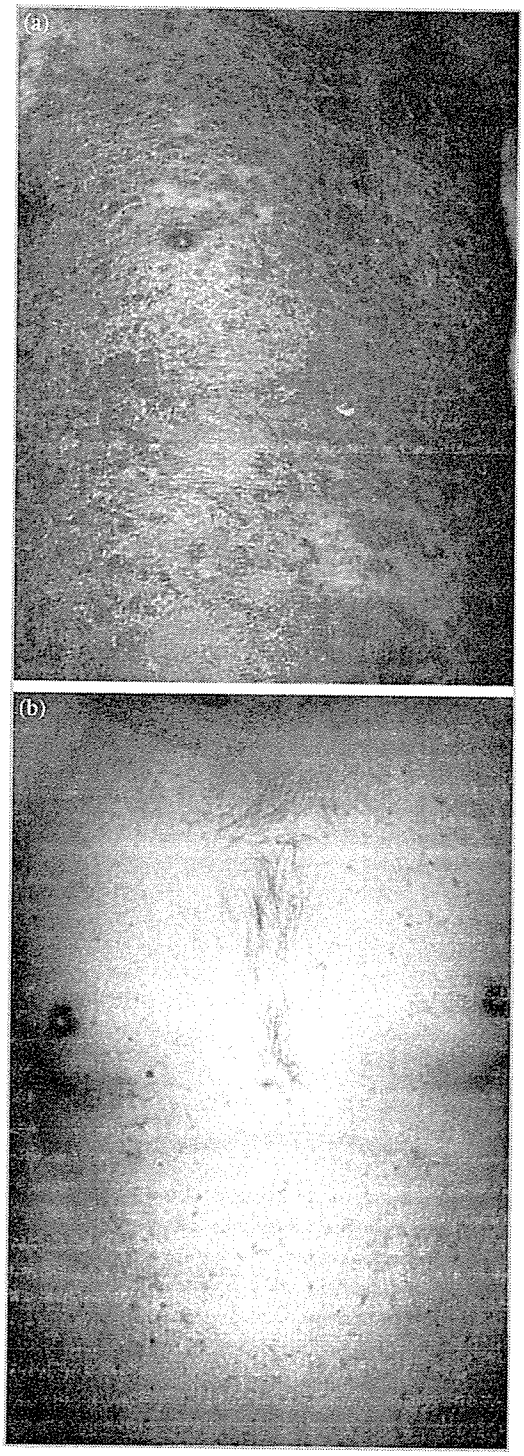

Fig 1. Clinical presentation of psoriatic erythroderma on admission (a) and resolution of psoriatic lesions after hepatitis (b).

One month after cessation of etretinate, he showed almost complete remission of psoriatic lesions on the trunk and extremities (Fig. 1b). No recurrence was observed during 3 months of follow up.

Materials and methods

After obtaining informed consent, peripheral blood T cells were taken at two different time points: during the peak of erythroderma and liver dysfunction (erythrodermic stage), and 1 month after complete clearance of psoriatic lesions, in which the liver dysfunction had returned to normal (resolution stage). Simultaneous flow cytometric assessments of T cell phenotype and cytokine synthesis were performed as previously described.[7] List mode multiparameter data files were analysed using the PAINT-A-Gate^{Plus} program. T cells were stimulated with phorbol myristate acetate and ionomycin for 4 h in the presence of brefeldin A, and were then examined for cytokine synthesis capacity at a single-cell level (CD8− gated and CD8+ gated T cells) by flow cytometry. Allophycocyanin-conjugated monoclonal antibodies anti-Leu4 (CD3), peridinin chlorophyll protein-conjugated anti-Leu2 (CD8), phycoerythin-conjugated anti-interferon (IFN)-γ, antitumour necrosis factor (TNF)-α, anti-interleukin (IL)-2, anti-IL-4 and anti-IL-13 were obtained from Becton Dickinson (San Jose, CA, U.S.A.). The cutaneous lymphocyte-associated antigen (CLA)-specific fluorescein isothiocyanate-conjugated rat monoclonal antibody HECA-452 was kindly provided by Dr Louis J. Picker (UT Southwestern Medical Center, Dallas, TX, U.S.A.).[8]

Results

The frequency of CD4+ T cells in circulating lymphocytes in the erythrodermic stage and the resolution stage was 55·0% and 49·0%, respectively, while that of CD8+ T cells in each stage was 20·6% and 19·0%, respectively. The results of cytokine synthesis capability of T cells in this patient showed that frequencies of IFN-γ-producing CD8+ T cells at the erythrodermic stage and IL-4-producing CD4+ T cells and CD8+ T cells at the resolution stage dramatically increased as compared with those of corresponding T cells in patients with psoriasis vulgaris in our previous studies (Fig. 2). When the frequencies of IFN-γ-producing CD4+ and CD8+ T cells obtained at the two stages were compared, those at the erythrodermic stage were increased. In contrast, the frequencies of IL-4- and IL-13-producing CD4+ and CD8+ T cells (IL-13, data not shown) were much higher at the resolution stage than at the erythrodermic stage (Fig. 2). There were no significant differences in TNF-α- and IL-10-producing cells between the two stages. When the frequencies of cytokine synthesis capabilities were analysed on CLA+ T-cell populations with skin-homing capacity, the difference between the two stages was more striking: a remarkable increase in the frequency of IL-4-producing cells was observed in a CLA+ T-cell fraction at the resolution stage compared with the erythrodermic stage (Fig. 3b,d). Conversely, the frequencies of IFN-γ-producing CD8+ T cells in a CLA+ T-cell fraction were remarkably increased at the erythrodermic stage (Fig. 3a,c). In contrast, no apparent difference was noted between the two stages when a CLA− T-cell fraction was analysed (Fig. 3). There

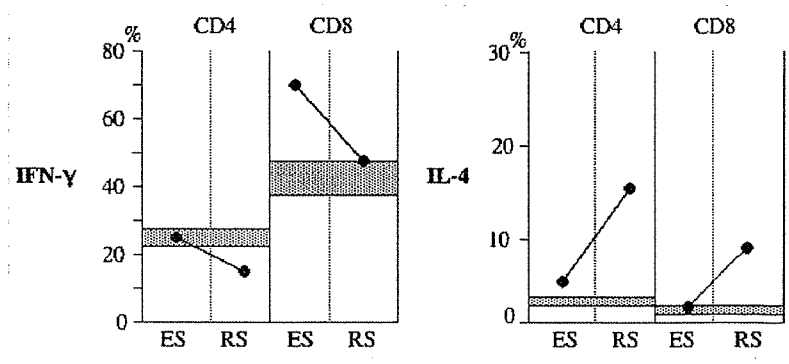

Fig 2. Comparison of frequencies of cytokine synthesis capabilities in CD4+ and CD8+ T cells between erythrodermic stage (ES) and resolution stage (RS). Cytokine synthesis capabilities in both CD4+ and CD8+ T-cell subsets in peripheral blood in 10 patients with psoriasis vulgaris[7] are indicated by grey zones. IFN-γ, interferon-γ; IL-4, interleukin 4.

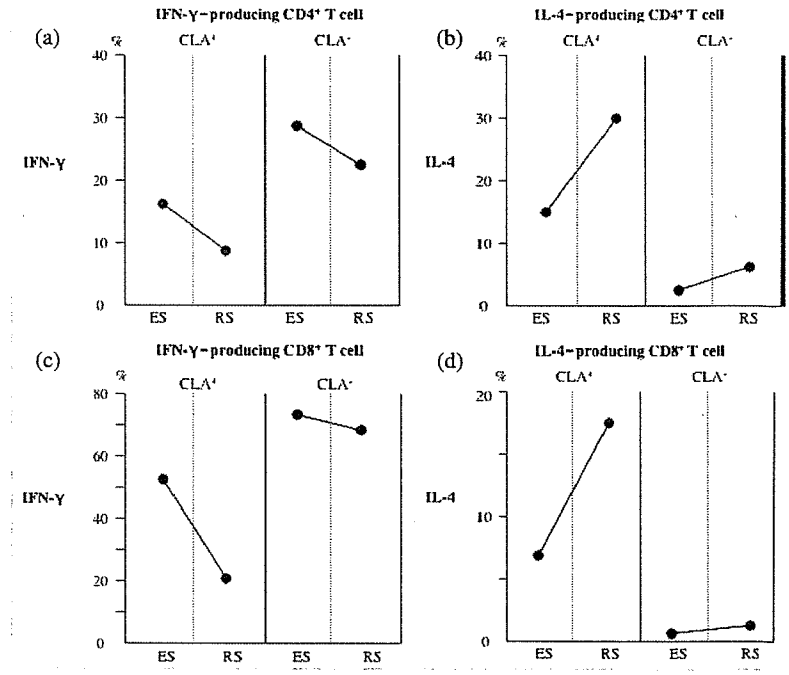

Fig 3. Frequencies of cytokine synthesis capabilities in cutaneous lymphocyte-associated antigen (CLA)+ and CLA− T-cell fraction in each CD4+ and CD8+ T-cell subset. Interferon (IFN)-γ-producing CD4+ T cells (a), interleukin (IL)-4-producing CD4+ T cells (b), IFN-γ-producing CD8+ T cells (c) and IL-4-producing CD8+ T cells (d). ES, erythrodermic stage; RS, resolution stage.

were no prominent differences in frequencies of TNF-α-producing-cells and IL-10-producing cells in a CLA+ fraction between the two stages.

Discussion

Clearance of severe psoriasis without treatment has been reported in a number of diverse physiological settings including removal of malignant tumours such as thyroid cancer,[9] and following allogeneic bone marrow transplantation[10] and agranulocytosis.[11] Such diversity might reflect the effects of certain cytokines released during these events. Indeed, several treatment modalities that can cause a type 1/type 2 cytokine shift in psoriasis have been shown to have beneficial effects in psoriasis: these include narrowband ultraviolet (UV) B therapy, psoralen plus UVA treatment and systemic vitamin D_3 derivatives.[12–14]

In our patient, complete clearance of severe intractable psoriatic erythroderma was temporally associated with recovery from acute hepatitis (induced by etretinate treatment) occurring with a shift in the type 1/type 2 cytokine balance to a type 2 response. Although etretinate administration itself could contribute to the alterations of cytokine balance,[14] its effects would be overwhelmed by the event of drug-induced hepatitis. Our case seems to indicate that alteration in a patient's cytokine profile may bring long-lasting remission of severe psoriasis because this patient has remained free of symptoms for several months without the use of any effective antipsoriatic agents.

Although it remains to be determined whether CD4+ or CD8+ T cells are primarily responsible for hyperproliferation and accelerated differentiation of keratinocytes, recent evidence has been convincingly presented that activation of T cells plays an important role in triggering and perpetuating the disease.[1–6]

Indeed, a dramatic increase in the frequency of IFN-γ-producing CD8+ T cells in peripheral blood was observed during the erythrodermic stage in this patient. Expansion of this subset would contribute to the deterioration of psoriatic erythroderma on the one hand and to liver damage, as evidenced by an increase in aminotransferase values, on the other. In support of this possibility, there are many reports demonstrating increased IFN-γ production by peripheral blood T cells not only in cutaneous drug reactions[15] but also in drug-induced hepatitis.[16] Thus, liver damage in this patient is likely to have been induced by etretinate, but not secondary to the development of erythroderma.

Although recent studies clearly demonstrated that virus-specific type 1 CD8+ T cells are responsible for persistent control of viraemia, they are not effective in chronic HCV infection because impaired functions such as cytotoxicity, proliferation capability and cytokine-producing potential of virus-specific CD8+ T cells have been documented:[17] CD8+ T-cell responses against HCV may be silenced *in vivo* due to a lack of important factors that can maintain CD8+ T-cell function, such as type 1 CD4+ T cells. Our finding of a dramatic decrease in serum HCV RNA after the development of hepatitis suggests that drug-induced activation of CD4+ T cells may represent a triggering factor that can stimulate otherwise dormant antiviral CD8+ T cells. A large amount of IFN-γ produced by expansion of IFN-γ-producing CD8+ T cells via its direct antiviral effect, acting synergistically with activation of antiviral cytotoxic T cells, may have contributed to the decrease in HCV RNA observed in this patient.

It has been shown that a balance of immune responses by type 1 and type 2 cytokines is critical in the development of psoriatic lesions.[2,6] In the present study, we demonstrated that complete clearance of psoriatic erythroderma was well correlated with a dramatic increase in the frequencies of type 2 cytokine (IL-4 and IL-13) producing CD4+ T cells and a concomitant decrease in the frequencies of IFN-γ-producing CD8+ T cells. Our previous studies showed that such dramatic type 2 predominance has been a rare event even in atopic dermatitis. These results clearly indicate that a shift towards type 2 predominance would contribute at least in part to the resolution of psoriasis. Moreover, in view of our previous study showing that there was little difference in frequencies of type 1 and type 2 cytokine-producing cells in stable psoriasis vulgaris compared with normal controls, our present observations might be interpreted as indicating that peripheral type 1 cytokine levels would increase prominently in active psoriasis such as psoriatic erythroderma and decrease to nearly normal levels as psoriasis becomes stable.[7]

In conclusion, our data indicate that the modulation of the balance between type 1 and type 2 responses is a target for future treatment of psoriasis. Indeed, recent studies have shown that agents such as IL-4 and fumaric acid esters, that can change the cytokine balance in favour of type 2 responses, induce clinical improvement of psoriasis.[14,18,19] Careful monitoring of the cytokine balance using simultaneous flow cytometric assessment of T-cell phenotype and cytokine synthesis would be useful for administration of immunomodulatory treatment of psoriasis.

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REVIEW ARTICLE

Drug-induced Hypersensitivity Syndrome(DIHS): A Reaction Induced by a Complex Interplay among Herpesviruses and Antiviral and Antidrug Immune Responses

Tetsuo Shiohara[1], Miyuki Inaoka[1] and Yoko Kano[1]

ABSTRACT

A relationship between viral infections and the simultaneous or subsequent development of allergic inflammation has often been observed in various clinical situations. Recent studies suggest an intimate relationship between reactivations of herpesviruses including human herpesvirus 6 (HHV-6) and the development of a severe systemic hypersensitivity reaction referred to as drug-induced hypersensitivity syndrome (DIHS). This syndrome has several important clinical features that cannot be solely explained by drug antigen-driven oligoclonal expansion of T cells: they include paradoxical worsening of clinical symptoms after discontinuation of the causative drug. In view of the similarity to GVHD or immune reconstitution syndrome (IRS) in clinical manifestations and emergence of viral infections, the clinical symptoms observed during the course of DIHS and GVHD are likely to be mediated by antiviral T cells that can cross-react with the drug and alloantigens, respectively. In considering common intrinsic properties of the causative drugs to potentially induce immunosuppression, reconstitution of a valid immune response to these viruses, which is typically observed in IRS, may be the most crucial process that takes place after withdrawal of the causative drug in patients with DIHS. Thus, this syndrome should be regarded as a reaction induced by a complex interplay among several herpesviruses (EB virus, HHV-6, HHV-7, and cytomegalovirus), antiviral immune responses, and drug-specific immune responses. This review includes discussion of the pathomechanism, the clinical symptoms, laboratory findings, pathological findings and therapy.

KEY WORDS

drug-induced hypersensitivity syndrome, GVHD, herpesviruses, HHV-6, NK cells

INTRODUCTION

A large body of evidence clearly shows that infections do play a role in the development of various allergic diseases, although the exact nature of their contribution is largely unknown.[1-3] Do they directly induce immune cell cross-reactivity with drug-modified host antigens? Alternatively, do they represent merely the trigger that sets off an otherwise subliminal allergy through the action of proinflammtory cytokines? Given their potential to activate innate and acquired immune responses, investigators have become very interested in the relationship between viral infections and allergic inflammation. For instance, a relationship between viral infection and the simultaneous or subsequent development of drug eruptions has been often observed in the clinical situation; and ampicillin rash during infectious mononucleosis and an increased risk for developing drug eruptions in AIDS are perhaps the best known examples of the relationship.[4,5] However, although a number of viruses have been reportedly associated with drug eruptions, no convincing evidence has linked a single viral agent with the subsequent risk of developing one disease

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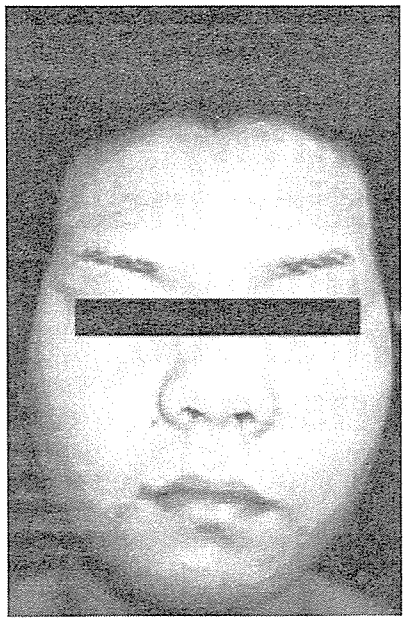

Fig. 1A Face of patient on his initial presentation demonstrates slight erythema.

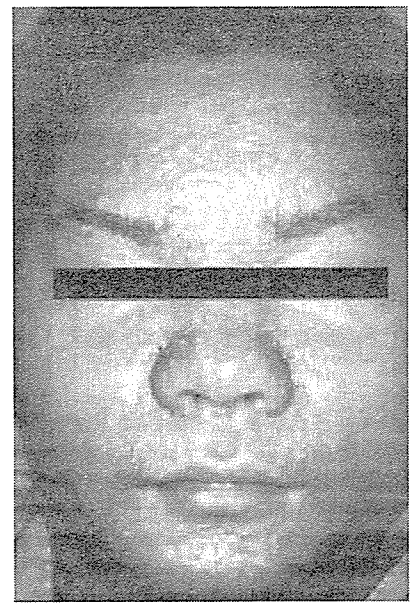

Fig. 1B Patient's face on admission three days after his initial presentation demonstrates edema, erythema studded with small pustules, and lymphademophy despite discontinuation of the causative drug.

Table 1 Drugs frequently causing DIHS/DRESS

· Carbamazepine	· Dapsone
· Phenytoin	· Salazosulfapyridine
· Phenobarbital	· Allopurinol
· Mexiletine	· Minocycline

outcome.

Nevertheless, recent studies including ours[6,7] suggest an intimate relationship between human herpesvirus 6 (HHV-6) and the development of a severe systemic hypersensitivity reaction referred to as drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic symptoms (DRESS).[8] In this review, we focus on the clinical symptoms of DIHS/DRESS and the possible etiologic role of herpes viruses including HHV-6 in the development of this syndrome.

CLINICAL SYMPTOMS

DIHS/DRESS usually occurs 3 weeks to 3 months after starting therapy with a limited number of drugs: they include carbamazepine, phenytoin, phenobarbital, dapsone, mexiletine, salazosulfapyridine, allopurinol, and minocycline (Table 1).[9] Cross-reactivity among these drugs has been frequently reported, because phenytoin, phenobarbital, and carbamazepine are metabolized to hydroxylated aromatic compound and arene oxides are suggested intermediates in the reaction.[10] DIHS/DRESS has no age or sex predilection. The delayed onset in relation to introduction of the causative drug is one of the important features of DIHS/DRESS that can be distinguished from other types of drug eruptions.

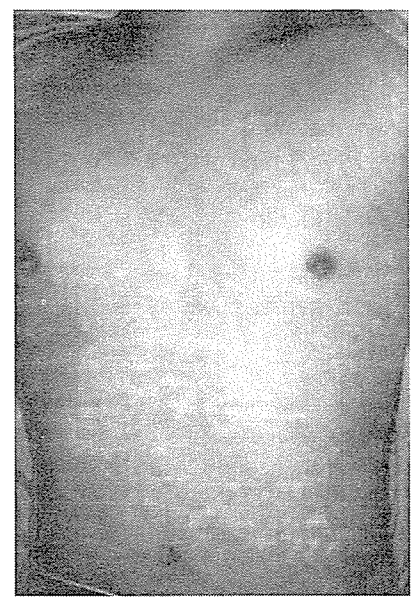

Fig. 2 Patient's chest and abdomen with confluent purpuric erythematous rash on admission, three days after discontinuation of the causative drug.

This syndrome commonly begins with a fever

Table 2 Diagnostic criteria for DIHS/DRESS

1. Maculopapular rash developing > 3 weeks after starting therapy with a limited number of drugs
2. Lymphadenopathy
3. Fever (> 38°C)
4. Leukocytosis (> 10×10^9/L)
   a. Atypical lymphocytosis
   b. Eosinophilia
5. Hepatitis (ALT > 100 U/L)
6. HHV-6 reactivation

The diagnosis is confirmed by the presence of five of the six criteria above

shortly followed by a maculopapular rash, which is usually pruritic, and variable degrees of lymphadenopathy. The temperature ranges from 38℃ and 40℃ with spikes that usually generate a concern of an underlying infection. The spiking fever often persists even for weeks despite discontinuation of the offending drugs. Initially, the upper trunk, face, upper extremities are affected and followed by involvement of lower extremities. Periorbital, facial or neck edema with pinhead-sized pustules is one of the characteristic features of DIHS/DRESS at the early stage (Figs. 1,2). The rash often generalizes into a severe exfoliative dermatitis or erythroderma. The severity of diseases at onset provides only a guide to prognosis and is not absolute. There is usually no mucocutaneous involvement, which helps distinguish DIHS/DRESS from other forms of severe drug eruptions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Tender lymphadenopathy can be seen in most patients early in the illness, affecting predominantly cervical nodes or generalized. Bilateral swelling of salivary glands with severe xerostomia is frequently observed at first visit. These finding suggest that reactivation of mumps virus may occur before onset of this syndrome. Hepatomegaly accompanied by splenomegalyis a common finding. The onset of these symptoms is highly variable; usually patients develop two or three features of symptoms followed by a step-wise development of other symptoms (Table 2). In many severe cases, these symptoms continue to deteriorate or several flare-ups can be seen even for weeks after stopping the offending drug. Interestingly, the more severe reactions often occur 3 days after withdrawal of the causative drug (Fig. 1A *vs* 1B). Such variability in the presentation and course of clinical symptoms allows for a delay in diagnosis, which can lead to significant morbidity.

Involvement of other organs varies, depending on the drug: allopurinol-induced DIHS/DRESS has more frequent renal involvement,[11] whereas there appears to be a higher risk of liver involvement in phenytoin or dapson-induced disease.[12] Other features of DIHS/DRESS include pneumonitis, coronary artery thrombosis, thyroiditis, rhabdomyolysis, encephalitis,[13-15] and diabetes mellitus.[16] Depending on the sites and severity of organ damages, various clinical symptoms would develop at various time points after onset. Nevertheless, in most cases their development is clinically silent and may be recognized only months or years later. In this regard, we have recently seen patients with DIHS/DRESS who developed limbic encephalitis and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) long after resolution of rashes. We have also seen patients with DIHS/DRESS who developed viral meningitis and herpes zoster 1–2 months after resolution of rashes. Thus, in the later phase, after an undefined period of critical illness of days to weeks, various organ failures will emerge. Despite withdrawal of the offending drug, resolution of symptoms in one organ is often followed by a step-wise development of such organ system failures (Fig. 3).

LABORATORY FINDINGS

Leukocytosis with atypical lymphocytes and eosinophilia of various degrees is also a prominent feature of this syndrome. Nevertheless, leukopenia and lymphopenia have been also reported[17] and they occasionally precede leukocytosis. Our analyses showed that atypical lymphocytes predominantly consist of activated $CD8^+$ T cells.[16] The eosinophilia may often be delayed for 1 to 2 weeks and occur even after elevations in liver enzyme return to baseline. The true frequency of eosinophilia may actually be lower (~ 60%) than previously reported.

Liver abnormalities occur in up to 70% of patients and are characterized by a marked increase in serum alanine aminotransferase value. Severe hepatitis portends a prolonged course characterized by multiple exacerbations and remissions of both rash and liver disease.[18,19] The hepatitis is usually anicteric; but if it is icteric, it tends to have a poorer prognosis.[20] Although the bilirubin may be normal at presentation, hyperbilirubinemia can develop even after the causative drug is discontinued.[12] Elevations in liver enzymes usually continue to persist for several days after discontinuation of the offending drug. The mortality from DIHS/DRESS can be approximately 20% and has been correlated with the degree of hepatic or renal involvement.

As we previously reported,[21] a dramatic decrease in serum IgG, IgA, and IgM levels is typically observed at onset and the lowest IgG, IgA, or IgM levels are usually detected several days after withdrawal of the offending drug. Thus, serum IgG levels seem to continue to decrease for at least several days after drug therapy is discontinued. Immediately after the nadir in the decrease, the overshoot in IgG levels is transiently observed within 1 to 2 weeks and they finally return to normal on full recovery. Another

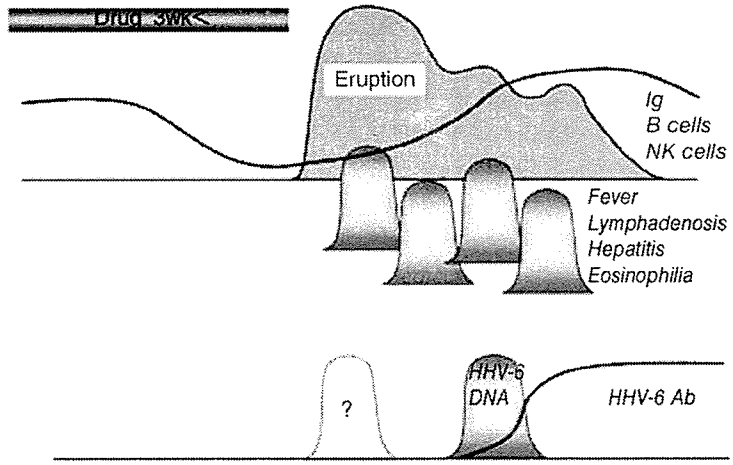

Fig. 3 The clinical course of DIHS/DRESS. This syndrome usually begins with a fever shortly followed by a maculopapular rash > 3 weeks after starting therapy with a limited number of drugs. Patients usually develop two or three features of symptoms followed by a step-wise development of other symptoms. These symptoms continue to deteriorate or several flare-ups can be seen even for weeks after stopping the offending drug. Despite such a wide variety of clinical symptoms, HHV-6 reactivation can be detected at the certain timing, 3 weeks after withdrawal of the causative drug.

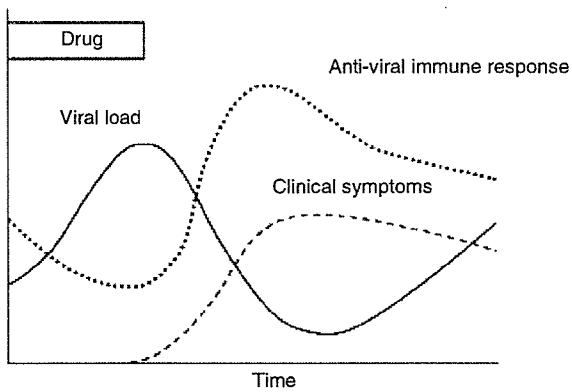

Fig. 4 Schematic figure illustrating the relationship among viral loads, anti-viral immune responses and clinical symptoms before and after discontinuation of the causative drug in DIHS/DRESS. Although a strong immune response to viruses is presumably beneficial in reducing viral loads, it may also have harmful consequences.Harmful aspects of this immune response are reflected in the clinical symptoms of DIHS/DRESS.

unique feature of this syndrome is unexplained cross-reactivity to multiple drugs with structures different from the offending drug which are used after onset of the symptoms.

Although close clinical similarities between DIHS/DRESS and infectious mononucleosis suggested a viral etiology, previous attempt to prove this etiology have failed; this is because previous studies ruled out the possibility that EB virus, cytomegalovirus (CMV), and hepatitis viruses could have produced the clinical syndrome or laboratory findings, solely based on serologic analyses. In this regard, we and Hashimoto's group reported an intimate relationship between HHV-6 reactivation and the development of this syndrome.[6,7] This would be the first example, in which the relationship between a single viral agent and the subsequent risk of developing one disease outcome has been convincingly demonstrated. It should be kept in mind, however, that HHV-6 reactivation as evidenced by the rise in HHV-6 IgG titers and HHV-6 DNA levels occurs generally 2–3 weeks after the onset of rashes in the vast majority of patients with DIHS/DRESS (Fig. 3). One may suppose, therefore, that HHV-6 reactivation is a consequence of cell activation occurring during the course of drug eruptions. Nevertheless, because HHV-6 reactivation can be detected in the vast majority of patients with DIHS/DRESS but not in other drug eruptions in Japan, this becomes a specific and sensitive diagnostic test to correct identification of all patients with this syndrome. This appears to be a gold standard test for DIHS/DRESS in Japan, which helps to confirm the identification of this syndrome. Recent studies including our own have also demonstrated that other herpesviruses, CMV, EBV, and HHV-7, can be se-

quentially reactivated during the course of this syndrome.[6,26-28] Based on these findings, we have proposed the concept that various herpes viruses may reactivate in sequential order during the course of DIHS/DRESS.[29]

To prove hypersensitivity to the causative drug, confirmatory testing such as patch tests and lymphocyte transformation tests (LTT) is often performed. The LTT is laboratory-based *in vitro* technology that is most widely available for the assessment of drug-reactive T cells.[22] Although these *in vivo* and *in vitro* tests are consistently positive in the vast majority of patients with DIHS/DRESS and negative in controls, contradictory results can be reported when performed during the acute stage[23-25]: false negative reactions are observed due to the early timing. Positive reactions can be consistently observed when tests are performed after remission, usually 4–6 weeks after onset. In particular, LTT become positive at least 4 weeks after onset and strong positive reactions can be observed even >1 year after discontinuation of the causative drug, a finding never observed in other severe drug eruptions, such as SJS. Considering the strong positivity long after resolution of the lesions, LTT appears more reliable and less cumbersome than patch testing, although the reported sensitivity of both tests are comparable.

PATHOLOGICAL FINDINGS

The common pathological findings are superficial perivascular lymphocytic infiltrates and some extravasated erythrocytes or eosionophils. A dense, band-like lymphocytic infiltrates with epidermotropism, suggestive of lymphoma, can be seen in some patients. In some patients, there is liquefaction degeneration of the basal cell layer with a lichenoid infiltrate, compatible with severe drug eruptions. However, this lichenoid infiltrates with apoptotic keratinocytes, a finding frequently seen in SJS and TEN, are relatively atypical findings in DIHS/DRESS. Immunohistochemical stains demonstrate a predominance of T cells.

In our first report on HHV-6 in a patient with DIHS/DRESS, we detected high levels of HHV-6 genome and viral antigens on infiltrating cells in the skin lesions taken at the early stage,[6] which suggests an etiological role of this microorganism. However, the presence of HHV-6 DNA in the lesions cannot be taken as proof of causation of the lesions; and we could not exclude the possibility that the detection of HHV-6 DNA in the cellular infiltrates could merely reflect a propensity for viral recurrence to lead to infection of these cells.

PATHOMECHANISMS

Although several theories have been proposed, the pathomechanisms of DIHS/DRESS remains largely unknown. So far, no satisfying explanation for diversity of the clinical symptoms as described above has been offered. The results of the patch tests and LTT indicate that drug-specific T cells are the driving force behind this syndrome.[6,21,30-32] However, not easily reconciled with drug antigen-driven oligoclonal expansion of T cells are clinical features, such as its delayed onset, frequent deterioration or several flare-ups after withdrawal of the causative drugs, multiorgan involvement, and unexplained cross-reactivity to multiple drugs used after onset of rashes. An alternative theory is that toxic oxidative metabolities of these drugs generated under certain circumstances bind to tissue macromolecules thereby acting as haptens stimulating $CD4^+$ and $CD8^+$ T cells.[10]

We have recently suggested an important role of herpesvirus reactivations sequentially occurring before and during the course of this syndrome in the development of DIHS/DRESS[29]: reactivation of latent herpesviruses, such as EBV, may be initially induced far before onset of clinical symptoms and strong immune responses to the reactivations might have the dual effects of reducing viral loads and developing clinical symptoms. According to this theory, clinical symptoms are likely mediated by an expansion of virus-specific and nonspecific T cells in response to the reactivations of these viruses. Indeed, in EBV-induced infectious mononucleosis, an increase in systemic viral loads is not reflected in symptom severity; the severity is rather a reflection of massive expansion of T cells. In this regard, we for the first time reported a patient who experienced severe skin rash associated with sequential reactivations of various herpesviruses.[29] Until now, however, longitudinal analyses of herpesvirus reactivations during the course of the syndrome have been predominantly performed by serologic tests, but not by PCR-based detection of viral DNA, which is obscured by uncertainty about the rise in antibody titers to viruses in this setting: reactivations of herpesviruses at the early phase cannot be reflected in antibody titers at the early phase because a dramatic decrease in Ig production has been reported to occur at that time.[21] We therefore performed real-time PCR to detect and quantify viral DNA, using blood samples sequentially obtained from patients with DIHS/DRESS after onset of rashes.

Although the order of herpesviruses sequentially reactivated was not exactly the same in patients with DIHS/DRESS examined, our PCR analyses showed that various herpesviruses can sequentially reactivate during the course of this syndrome (Kano Y *et al.* Manuscript submitted). The cascade of virus reactivation initiated by HHV-6 or EBV extended, with some delay, to HHV-7 and eventually to CMV. Surprisingly, this cascade of sequential herpesvirus reactivations observed in DIHS/DRESS is quite similar to that observed in graft-versus-host disease (GVHD).[33,36] In view of the similarity between DIHS/DRESS and

GVHD with regard to the clinical manifestations, the highly variable waxing and waning nature of the clinical manifestations occurring in different organs despite discontinuation of the offending drug could be explained by sequential reactivations of these herpesviruses; nevertheless, sequential reactivations of these viruses were not always associated with evidence of overt clinical symptoms. Interestingly, recent studies have provided strong suggestive evidence for a role of viral infections in the emergence of alloreactive T cells and the development of GVHD.[33-35] In the setting of GVHD, it has been hypothesized that activation of donor-derived antiviral T cells by alloantigens or bystander activation of the antiviral T cells by massive cytokine production are responsible for the development of GVHD. In support of this hypothesis, herpesvirus genome can be detected at high frequency coincident with the clinical symptoms, suggesting that virus-driven clonal expansions of alloreactive T cells that may have originally generated to deal with herpesviruses are involved in initiating GVHD[37]: if so, the severity of clinical symptoms in DIHS/DRESS as well as GVHD would be determined by the magnitude of expansions of antiviral T cells. These similarities to GVHD, together with the ability of HHV-6 and HHV-7 to reactivate heterologous viruses,[38,39] led us to consider the possibility that these herpesviruses might be functionally linked *in vivo*, the reactivation of one leading to the reactivation of the other, thus explaining the ambiguity in the apportioning their role. These considerations raise the possibility that the clinical manifestations originally attributed to CMV or EBV can be ascribed to HHV-6 or HHV-7.

Thus, by analogy with the similarities to GVHD, the clinical symptoms observed during the course of DIHS/DRESS are likely to be mediated by antiviral T cells that can cross-react with the drugs but not solely by drug-driven oligoclonal expansions of drug-specific T cells. This scenario could provide answers to many questions arising on DIHS/DRESS: why frequent deterioration can be seen after withdrawal of the offending drug; why multiple organs are involved in a sequential order; and why unexpected cross-reactivity to multiple drugs with different structures can be seen despite a very limited number of drugs responsible for initiating this syndrome. Our unpublished finding that LTT to the offending drug was negative during the development of rash and became strong positive after recovery (Manuscript in preparation) could be also explained by this scenario, because these herpesviruses could induce and maintain a potent specific memory T-cell response for long times after recovery from DIHS/DRESS due to their common properties of ubiquitous prevalence in human populations and the capacity to grow in lymphoid cells.

Assuming that antiviral T cells are primarily involved in the development of DIHS/DRESS, the question arises why viral genome was only detected 2–3 weeks after onset of this syndrome but not at the early stage. In this regard, of note are previous reports indicating that causative drugs shown to induce DIHS/DRESS have in common intrinsic properties to potentially cause immunosuppression.[21] In view of these properties of these drugs, our finding that paradoxical worsening of clinical and laboratory parameters was often observed after discontinuation of the causative drug in many patients with DIHS/DRESS[6,21] can be alternatively interpreted as follows: discontinuation of these drugs could be associated with rapid restoration of virus-specific cellular and humoral responses that would reduce viral loads on the one hand but cause tissue damage on the other (Fig. 4). Thus, unrecongnized reactivations of herpesviruses would be already present by protracted administration of these drugs before onset of this syndrome and this reactivation may be only unmasked by rapid restoration of anti-viral immune responses due to discontinuation of these drugs. In support of this possibility, many cases with various pathogens-associated immune reconstitution syndrome (IRS) have been reported to occur in HIV-infected individuals after administration of potent antiretroviral therapy or withdrawal of immunosuppressive agents that can cause improved anti-viral immune responses.[40] Unlike the widely held notion, clinical symptoms in DIHS/DRESS are likely to be mediated by rapidly restored anti-viral immune responses, just like those in IRS, but not by viruses themselves. Thus, our finding of no detection of viral genome at the time of clinical onset[21] can be explained by assuming that virus clearance may take place upon reconstitution of a valid immune response after withdrawal of the causative drug in patients with DIHS/DRESS.

TREATMENT

Early recognition of this syndrome is the most important step in treatment and is essential in improving patient outcomes, because many physicians are not familiar with this syndrome. Empirical treatment with antibiotics or NSAIDs should not be done during the acute period, which may confuse or worsen the clinical picture probably due to unexplained cross-reactivity.

The mainstay of treatment is systemic corticosteroids. Rapid resolution of rashes and fever occurs within several days after starting systemic corticosteroids: the usual dosage is prednisolone 40–60 mg/day. Nevertheless, this treatment has not been formally studied in randomized placebo-controlled trials; however, this trial is difficult to perform due to the life-threatening nature of this syndrome. Systemic corticosteroids need to be tapered over 6–8 weeks to prevent the relapse of various symptoms of this syn-

drome. Marked deterioration of various symptoms is often observed with accidental discontinuation or too rapid tapering of corticosteroids. We therefore recommend that all patients with DIHS/DRESS be hospitalized even if the initial presentation is mild. If symptoms deteriorate despite systemic corticosteroids, other options used successfully in small series of patients include pulsed intravenous methylprednisolone (30 mg/kg for 3 days), intravenous immunoglobulin G (IVIG), and plasmapheresis, or a combination of these. It should be further noted that these immunosuppressive therapies may enhance the risk of infectious complications and sepsis. Mild cases may recover from this syndrome by supportive care without the need of systemic corticosteroids within few weeks. Even in these mild cases, however, hepatic and renal value should be monitored closely and appropriate testing should be performed to exclude involvement of specific organs, such as lungs, heart, and thyroid, known to be affected by this syndrome. In particular, because hypothyroidism may appear for several months after the acute illness is completely resolved, thyroid function should be monitored carefully for at least several months after resolution of the acute illness.

CONCLUSION

Although great strides have been made in our understanding of the natural history and pathomechanism (s) of this syndrome, many questions remain unanswered. DIHS/DRESS should not be regarded as a reaction solely mediated by drug antigen-driven oligoclonal expansion of T cells, but as a reaction induced by a complex interplay among viruses, antiviral innate and adaptive immune responses, and, of course, drug-specific immune responses. Thus, DIHS/DRESS provides a fascinating model for studying the complex interplay leading from viral infection to the development of allergic diseases.

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Hypogammaglobulinemia as an early sign of drug-induced hypersensitivity syndrome

To the Editor: We read with great interest the article by Nishimura et al[1] in the November 2005 issue of the Journal. In this article, the authors described a patient with clomipramine-induced hypersensitivity syndrome in whom lower serum immunoglobulin levels were evident in the early stage of disease and returned to normal range at the recovery stage, although special attention was not given to this point. We would like to add our findings regarding serum immunoglobulin levels observed in patients with allopurinol hypersensitivity syndrome.

Drug-induced hypersensitivity syndrome (DIHS)/drug rash with eosinophilia and systemic symptoms (DRESS) is a severe multiple-organ system reaction caused by specific drugs, such as anticonvulsants, salazosulfapyridine, and allopurinol. Although reactivation of human herpesvirus 6 (HHV-6) has been demonstrated during the course of DIHS/DRESS, the pathogenetic mechanism of this reaction remains unknown. In this regard, we have demonstrated that patients with anticonvulsant hypersensitivity syndrome showed a decrease in serum immunoglobulin and circulating B cells at onset; we have suggested that a drug-induced transient immunodeficiency might be a prerequisite for the development of DIHS/DRESS via reactivation of HHV-6.[2] In support of this, several articles have demonstrated a transient hypogammaglobulinemia at onset in patients with DIHS/DRESS.[3,4] We examined whether a similar decrease in immunoglobulin levels could be detected at onset in patients with allopurinol hypersensitivity syndrome.

Table I. Serum immunoglobulin levels at onset in patients with allopurinol hypersensitivity syndrome

Group	Immunoglobulin (mg/dL) IgG	IgA	IgM
Reference range	778-1793	80-413	37-254
Patients with AHS (n = 4) (mean ± SD)	789 ± 164*	156 ± 68†	111 ± 42‡
Control patients (n = 9) (mean ± SD)	1263 ± 187	310 ± 108	75 ± 27

AHS, Allopurinol hypersensitivity syndrome; *Ig*, immunoglobulin; *SD*, standard deviation.
*$P < .005$ versus control in IgG levels.
†$P < .05$ versus control in IgA levels.
‡$P = .09$ versus control in IgM levels.

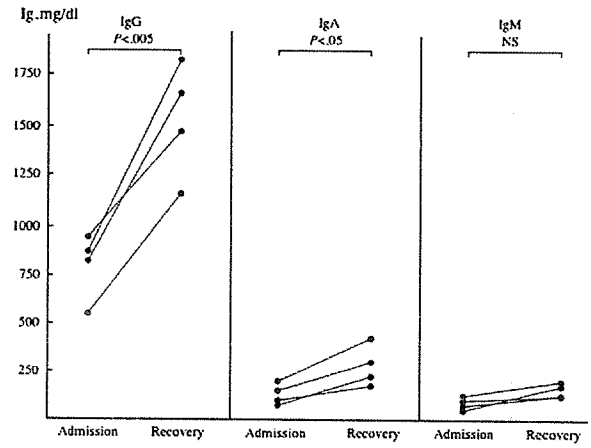

Fig 1. Serum immunoglobulin levels on admission and full recovery in patients with allopurinol hypersensitivity syndrome. *P* values were determined by *t* test for comparison between admission and recovery.

Four patients with DIHS/DRESS induced by allopurinol (2 men, 2 women; mean age, 56.2 years; age range, 41-67 years) were enrolled in this study. The duration between drug introduction and onset of rashes ranged from 29 to 39 days (mean, 32.2 days). All patients were treated with systemic corticosteroids. Nine patients who had been taking allopurinol for more than 5 months without any adverse reactions served as control subjects. Serum samples for evaluation of serum immunoglobulins were taken from patients with allopurinol hypersensitivity syndrome at onset and after full recovery. The IgG and IgA levels were markedly decreased at onset compared with those of control patients (Table I). The decreased immunoglobulin (IgG and IgA) levels

returned to normal range after complete recovery (Fig 1). A more than 4-fold increase in anti-HHV-6 IgG titers was detected at more than 3 weeks compared with those at onset in all patients. No significant increases in anti-HHV-6 IgG titers were observed in the control patients.

Our results concerning serum immunoglobulins were consistent with those of the patient observed in the article by Nishimura et al.[1] Considering that clomipramine has been shown to have immunomodulatory effects on B cells[5] similar to those of allopurinol,[6] anticonvulsants, and salazosulfapyridine, it is likely that the immunomodulatory effects of the drugs, regardless of each pharmacological action, may contribute to the development of DIHS/DRESS. Our observations, together with previous reports and the article by Nishimura et al, suggest that DIHS/DRESS could be induced in susceptible patients in which B cells might be harmfully affected by long-term administration of the specific drugs with immunomodulatory potentials. These immunologic alterations subclinically induced by protracted administration of the causative drugs may primarily contribute to the initial herpesvirus reactivation, such as HHV-6. One may well miss this diagnostic marker since changes may be evident only when laboratory values are compared at onset and after full recovery.

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Dermatoscopy, not dermoscopy!

To the Editor: In the "Contents" of the Journal for February 2006 (volume 54, No. 2, page 12A), under "Case Reports," are two articles, back to back, one titled, "Clinical and dermatoscopic fading of post-transplant eruptive melanocytic nevi after suspension of immunosuppressive therapy" and the other "Dermoscopy for 'true' amelanotic melanoma: A clinical dermoscopic-pathologic case study." I write to call attention to the fact that there are no "true" words "dermoscopy" and "dermoscopic"; the words correct are "dermatoscopy" and "dermatoscopic." And that is precisely why disciplines are names dermatology, not dermology, and dermatopathology, not dermopathology.

The entry for *dermat-, dermato-* in "A Dictionary of Dermatological Words, Terms, and Phrases" by Leider and Rosenblum (Dome Laboratories, West Haven, Conn; 1976; revised edition) reads as follows: "combining forms from the stem of the Greek word *derma,* skin, *dermatos,* of the skin." Not surprisingly, there is no entry in that dictionary for *dermo* because no such stem exists.

It probably is much too late to rectify "keratinocyte" by "keratocyte" (fortunately, whoever spawned "melanocyte" had the good sense not to designate it "melaninocyte"), but it is not too late to banish dermoscopy and dermoscopic in favor of dermatoscopy and dermatoscopic.

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Drug eruptions to contrast media in Japan

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Summary

Background. In Japan, drug eruptions to nonionic iodinated contrast media have been reported since the products appeared on the market in 1986.

Objectives. To evaluate this clinical finding, we analysed the number of patients with drug eruption to contrast media in our hospital from 1989 to 2003.

Methods. In total, 117 patients suspected of such drug eruptions were patch and intradermal tested with contrast media (as commercially sold). Those who tested positive were evaluated.

Results. Of the 117 patients, 69 patients (19 men; 50 women, mean ± SD age 51.4 ± 16.5 years, range 17–86) showed positive reactions to contrast media. The number was 6–13 annually from 1989 to 1995, and 1–4 annually from 1996 to 2003.

Conclusion. Although our data suggest (but do not prove) that patients with drug eruption to contrast media decreased in number, this condition is still not rare in Japan. Higher annual exposure to contrast media, including pretesting, could play an important role in this observation.

Contrast media is of two types: high-osmolar ionic and low-osmolar nonionic. Of the nonionic iodinated contrast media available in Japan, Iopamidol appeared on the market in 1986 and iohexol in 1987, and subsequently six more products (four monomers and two dimers). Monomers are mainly used, while dimers are available only for myelography and angiography. The prevalence of adverse reactions to ionic and nonionic contrast media was 12.66% and 3.13% in a nationwide comparative clinical study.[1] The study reported that most frequent symptoms of adverse reactions to nonionic contrast media were nausea (1.04%), heat sensation (0.92%), urticaria (0.47%) and itching (0.45%), and about 70% of such reactions occurred during or within 5 min of injection. Shortly after their introduction, many cases of drug eruption to contrast media were also reported.[2,3] We encountered 59 cases of drug eruption to contrast media between 1989 and 1997.[3] Clinical features were papulomacular eruption: oedematous erythemas and papules, mainly on the trunk (Fig. 1).[2,3] In most patients without history of sensitization to contrast media, the eruption occurred 6 days after the administration, and of those previously sensitized to the media, the eruption occurred from several hours to 1 day after administration.[3] To evaluate this clinical finding, we analysed the drug eruptions to contrast media in our hospital in the period 1989–2003.

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Patients and methods

In total, 117 papulomacular eruption patients suspected of having drug eruption and 8 normal healthy volunteers were patch and intradermal tested with 4 nonionic monomers (iopamidol, iohexol, ioversol, and iomeprol, as commercially available). Although we encountered

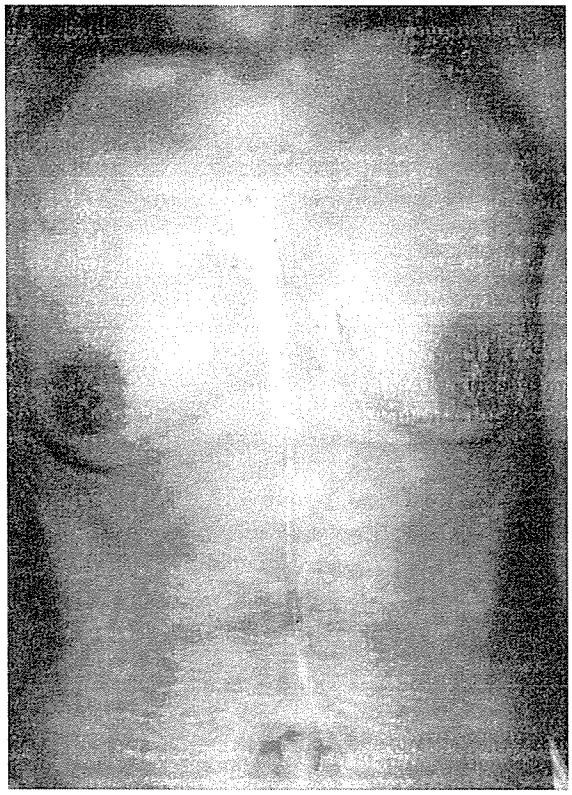

Figure 1 Clinical feature of drug eruption to contrast media: oedematous erythemas and papules mainly on the trunk.

seven patients (one man and six women) showing urticaria during or within 30 min of injection, these seven patients were not included as they were not patch and intradermal tested.

Patch testing

Media were applied on the back with vinyl plaster (TORII® patch tester; Torii Pharmaceutical Co., Ltd, Japan) for 2 days, and the results were read with the ICDRG scoring system[4] 3 days after application. Reactions of + to +++ were regarded as positive.

Intradermal test

Each medium (0.05 mL) was injected onto the dermis on flexor aspect of the forearm, and test sites were observed 24 h after injection. An erythematous reaction > 20 mm in diameter was regarded as positive.

Patients revealing positive reactions of patch and/or intradermal test were regarded as having drug eruption to contrast media.

Table 1 Results of patch testing to contrast media.

Score (ICDRG scoring system)	No. of patients
–	6
?+	13
+	43
++	7
Total	69

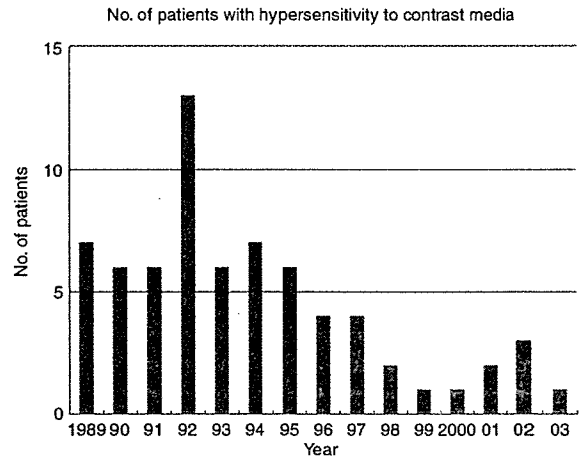

Figure 2 No. of patients with drug eruption to contrast media.

Results

Of the 117 patients suspected of having drug eruption to contrast media, 69 [19 men and 50 women, mean ± SD age 51.4 ± 16.5 years, range 17–86 years (mean ± SD age 50.7 ± 16.6 years for the men, 51.6 ± 16.6 years for the women)] were positive on intradermal test to contrast media, and these reactions occurred from several hours to 1 day after injection. Of these 69, 50 (72.5%) were patch test-positive and 13 (18.8%) showed weak reactions (?+ with ICDRG scoring system) to contrast media (Table 1). Eight volunteers were patch and intradermal test-negative. Figure 2 shows the number of patients annually in 1989–2003; there were 13 patients in 1993, and >6 patients annually from 1989 to 1995. After 1996, there were fewer than 4 annually.

Discussion

It has been speculated that deficiency of aldehyde dehydrogenase (ALDH)-2, a migrating isoenzyme of liver acetaldehyde dehydrogenase (low Km for acetaldehyde),[5] is a possible explanation for drug eruption to contrast media in Japan.[6] Deleted ALDH2, frequently

seen in East Asian populations and in 50% of Japanese,[7] leads to raised blood acetaldehyde levels associated with flushing syndrome.[8] It is suggested that accumulated acetaldehyde introduces degranulation of basophils or mast cells, and histamine release, and subsequently could lead to higher ability of contrast agents.[9]

Additionally, we speculate annual contrast media exposure could play an important role in drug eruption. Table 2 shows the number of diagnostic machines in eight countries from 2001 OECD health data. Japan had by far the highest number of computed tomography (CT) scanners and magnetic resonance imaging (MRI) scanners, with 84 CT scanners per million population and 23 MRI units.[10] These numbers are higher than other countries, as the average number of CT and MRI scanners in OECD countries was 17.7 and 6.5, respectively.[10] Berrington de Gonzalez reported that Japan had the highest annual X-ray frequency in a group of 15 countries.[11] Hence, it is possible that Japanese have more likely to be administered contrast media than people in other countries, and this increase in administration may increase sensitization.

In this respect, pre-testing with a small amount of contrast media, widely performed in Japan (incidence of pretesting was 76.7% in 1986–1988[12]) may increase exposure. Pretesting is typically preformed < 7 days before the administration of the full dose is due.[13] The Japanese Committee on the Safety of Contrast Media has repeatedly reported since 1989 that pretesting cannot predict severe adverse reactions,[12,13] yet, despite these reports, a test ampoule containing a small amount of contrast media only for pretesting was provided in the product packs in Japan until 2000. Although the incidence of pre-testing was decreasing, it was still 27.5% in the report in 2000.[12] Pretesting itself was not deemed a common cause of sensitization, as those who developed eruptions 6 days after administration seemed not to have been presensitized. However, pre-testing gives patients another opportunity to receive the media. The possible decrease of patient number in the past 6 years could relate to the decrease of pretesting (Fig. 2).

Table 2 Number of scanners per 1 million population (from OECD health data 2001).

Country	CT	MRI
Japan	84.4	23.2
Austria	25.8	10.9
Germany	17.1	6.2
USA	13.2	7.6
Sweden	13.8	6.8
Canada	7.3	2.5
Hungary	5.2	1.5
Mexico	2.0	0.3

Another possibility is that the sensitization occurred from contrast media-like chemicals with halogenated benzene rings, e.g. pesticides, fungicides, or herbicides.[9] It is unlikely, however, that the Japanese have more opportunities for such exposure. In addition, most patients seemed not to have been sensitized before administration, as mentioned previously.

Why such reactions occurred 6 days after administration is unclear. It is not a classic IgE response, but mainly a T-cell-mediated reaction.[14] We speculate the possible existence of chemical contaminants, which provoke delayed allergy-like reactions.

Intradermal test and patch testing were useful to diagnose this condition.[15] Contrast media themselves are not deemed irritant because patch test positivity was seen in 50 of 117 patients. Until a significant number of normal subject intradermal plus patch test controls become available, the diagnosis rests on: (i) dosing (ready documented), (ii) clinical appearance (morphology plus distribution), and (iii) time course (~6 days). We do not have data on provocation test[16] with contrast media, but we encountered one case of intradermal and patch test positivity who redeveloped drug eruption on repeat exposure. However, the significance of intradermal test and patch testing is controversial as there were many crossreactions among nonionized contrast media.[15] Thus, much remains to be clarified about the pathogenesis of such reactions.

In conclusion, we speculate that higher annual exposure, including pretesting, to contrast media, and a deficiency of ALDH2 play a role in drug eruption to contrast media in Japan. Although the number of patients may have decreased as reported here, this condition is still not rare in Japan. As patient referral patterns and actual number of doses used could not be documented, we consider this suggestive rather than a definitive conclusion.

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