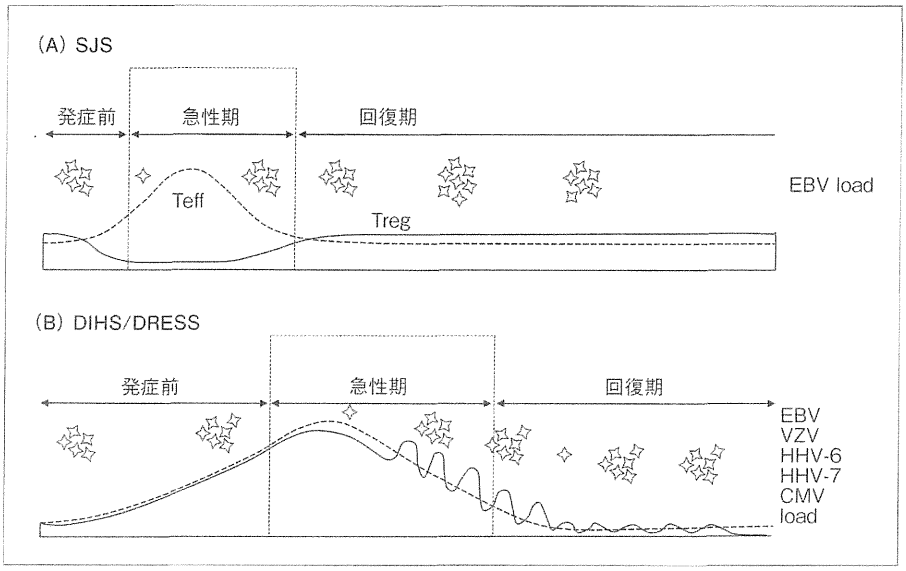

図 2　DIHSの発症機序

原因薬剤の投与により，Teff だけでなく Treg の増加が起こる結果として発症までに時間を要する．Treg の増加は潜伏ウイルスの再活性化を生じ，それがウイルス特異的 T 細胞のさらなる活性化をもたらす．

傷害を認めるものの，その傷害は限局的であり，TEN に近い症状を呈することはあっても通常 TEN に進展することはない．この所見は FDE では SJS/TEN ではみられない抑制機構が働いていることを示唆している．そこで，原因薬による誘発後の FDE の病変部を経時的に生検し，どのような細胞が浸潤してくるかを検討した．その結果明らかになったのは，FDE では正常の抑制機能をもつ Treg が誘発後早期に病変部に浸潤してくることであった(Mizukawa ら，投稿準備中)．このような Treg の速やかな遊走には，病変部局所に集積している肥満細胞[10]が重要な役割を果たしている可能性がある．このような Treg の病変部表皮に向けての遊走は FDE では辺縁部表皮に著明に生じるのに対し，TEN ではこれが生じないために $CD8^+$Teff 細胞による著明な表皮の傷害が起こると考えられた．

DIHSの発症機序

DIHS は，経過中にヒト 6 型ヘルペスウイルス(HHV-6)の再活性化を特徴的に認める重症薬疹の特殊型である[11,12]．SJS/TEN と異なり表皮の傷害はほとんどみられず，発症も遅発性で原因薬剤を中止しても寛解・増悪を繰り返し，遷延した経過をとる．しかも通常，DIHS では薬剤を抗原として用いた *in vitro* のリンパ球刺激試験(drug-induced lymphocyte stimulation test：DLST)は急性期にかならず陰性となり，2 カ月以降，強陽性となる[13]．これは通常の薬疹や SJS/TEN ではまったく認められない所見であり，この所見こそ，この特殊な臨床型の発症機序を考えるうえで特筆すべき所見なのである．この DLST が陰性の時期に HHV-6 の再活性化がみられるという事実を考えると，この時期に Treg が増加しているのではないかと推測できる．結果はまさにそのとおりのことが DIHS の急性期には起こっていたのである[9]．

DIHS を特徴づけている所見の数々は，Treg が特徴的に増殖していることにより説明できる．DIHS 患者の急性期 PBL から Treg 分画を除去して薬剤抗原で刺激すると，原因薬剤特異的にインターフェロン γ(IFN-γ)や TNF-α の産生が起こることから，この Treg の増加がエフェクター T 細胞(Teff)の活性化を抑えていることがわかった．さらに，急性期 PBL から Teff と Treg 分画を分離し，両者を一定の比でミックスした後刺激

し，Tregの機能をみたところ，健常コントロールと変わらない機能を有していることが明らかになった．つまり正常機能を有するTregが増加することによりTeffの活性化が抑制される結果，発症までに時間がかかり，その間に潜伏しているHHV-6などのヘルペス科ウイルスの再活性化が生じる可能性が示唆された(図2)．DIHSの病変部局所においても，Tregが増加する結果として，$CD8^+$ T細胞による表皮の著明な傷害は生じないことになる．

DIHSと免疫再構築症候群

免疫再構築症候群(immune reconstitution syndrome：IRS)の本来の定義は，AIDS患者にHAART療法を行った際に生じてくる免疫の回復に応じて起こる，さまざまな感染症様症状のことを指す．つまり免疫反応が抑制されているときには病原体が増加しても何ら臨床症状を示さないが，免疫の回復とともにそれらの病原体に対する免疫反応が活性化し，一見感染症が増悪したかのような症状を呈するようになる現象を指すもので，帯状疱疹やサイトメガロウイルス(CMV)感染症などのさまざまな日和見感染症がこれに含まれる[14]．このようなIRSはAIDS患者だけでなく，ステロイドなどの免疫抑制剤や化学療法，生物学的製剤などを中止あるいは減量後にも生じる．むしろ実際の臨床ではこのような状況で生じるIRSのほうが多いと考えてよい．サルコイドーシスもIRSの一症状として生じることが知られている．

DIHSの臨床経過や検査所見などを細かく検討してみると，IRSにきわめて近い免疫応答の回復が発症後にみられることがわかる．実際，DIHS同様，IRSにおいてもTregの増加が認められる．このようなDIHSの治療としてステロイドの全身投与を選択した場合にはDIHSそのものがIRSの病態に相当することもあり，ステロイドの減量のたびにIRS様の病態が生じることになる．これが典型的にみられるのがDIHSの際のCMVの再活性化である．CMVの再活性化はステロイドを用いている症例に生じやすく，しかもその減量時に生じやすいことを著者らはすでに明らかにしている[15]．

おわりに

本稿ではスペースの関係で，ある薬剤をまったく内服していない個人に，なぜその薬剤に特異的に反応するT細胞が存在するのかという基本的な疑問にはあえて触れなかったので，それについては拙著[16,17]を参照いただきたい．

薬疹は，いまやウイルス感染症や自己免疫疾患を巻き込んだ，きわめてダイナミックに拡大しつづける病態[17]であるとの認識をもつ必要がある．ウイルスの関与が明らかにされてから早10数年が過ぎたが，つぎの10年にはどのような飛躍が待っているのであろうか．

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Drug-Induced Hypersensitivity Syndrome: Recent Advances in the Diagnosis, Pathogenesis and Management

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Abstract

Drug-induced hypersensitivity syndrome (DIHS), also referred to as drug reaction with eosinophilia with systemic symptoms, is a life-threatening multiorgan system reaction caused by a limited number of drugs such as anticonvulsants. This syndrome is characterized by fever, rash, lymphadenopathy, hepatitis, and leukocytosis with eosinophilia. DIHS has several unique features that include the delayed onset, paradoxical deterioration of clinical symptoms after withdrawal of the causative drug and unexplained cross-reactivity to multiple drugs with different structures. Because of these features and a lack of awareness of this syndrome, DIHS is undoubtedly underdiagnosed in many countries despite its worldwide distribution. The clinical variability in the presentation and course of clinical symptoms of DIHS could now be interpreted as an indication that several herpesviruses reactivate in a sequential manner independently in the different organs. Dramatic expansions of functional regulatory T (Treg) cells observed in the acute stage would serve to induce such sequential reactivations of herpesviruses while a gradual loss of Treg function occurring after resolution of DIHS could increase the risk of subsequently developing autoimmune disease. Although systemic corticosteroids are the mainstay of treatment, it remains to be determined whether this treatment is beneficial from a viewpoint of disease outcome and sequelae.

Essentials in a Nutshell

- Drug-induced hypersensitivity syndrome (DIHS) is also referred to as drug reaction with eosinophilia with systemic symptoms (DRESS)
- DIHS is a rare, but probably underdiagnosed adverse drug eruption with an estimated incidence of 10 per million person-years
- DIHS is a severe life-threatening multi-organ system reaction caused by a limited number of drugs the most frequent of which are anticonvulsants

- DIHS is characterized by fever, rash, lymphadenopathy, hepatitis, and leukocytosis with eosinophilia
- The pathogenesis involves the reactivation of herpesviruses (HHV-6, HHV-7, Epstein-Barr virus – EBV, cytomegalovirus – CMV), an oligoclonal expansion of activated memory CD8+ T cells that can specifically recognize herpesvirus antigens, and an expansion of Treg cells

Introduction

Severe drug eruptions encompass several distinct clinical entities, the most serious being toxic epidermal necrolysis (TEN). TEN and DIHS represent the opposite ends of a spectrum of severe drug eruptions: the two diseases differ in clinical presentation as well as histological findings, prognosis and pathomechanisms, although the same drugs can often cause these diseases. Although the incidence of DIHS was considered to be less than that of TEN and Stevens-Johnson syndrome (SJS), whose incidence ranges from 0.4 to 1.2 and 1.2 to 6 per million person-years, respectively [1], its incidence continues to increase worldwide probably due to better recognition of this syndrome by doctors or improved population-based surveillance.

The first description of this syndrome is generally credited to Meritt and Putnam, who in 1938 described the toxic symptoms caused by therapy with phenytoin and noted that the symptoms could be divided into two cutaneous reactions: the first one being a mild morbilliform eruption that healed when phenytoin was withdrawn without relapses, and the other being a severe exfoliative dermatitis with fever and eosinophilia [2]. By the time Chaiken et al. [3] described the systemic implications of the second, the link with lymphadenopathy and multivisceral involvement such as hepatitis was established. Since then, there had been many case reports describing similar symptoms induced by relatively long-term therapy with various anticonvulsants, under several different names including phenytoin hypersensitivity syndrome, based on names referring to the causative drug. Bocquet et al. [4] proposed the term 'drug reaction with eosinophilia and systemic symptoms (DRESS)' for this disorder to distinguish it from other severe drug eruptions. This syndrome was independently recognized as a new and distinct disorder in the late 1990s by us [5] and Hashimoto's group [6]: our reports describing an intimate relationship between the development of this disorder and reactivation of HHV-6 rekindled interest in the disorder in Japan [5, 6]. The clinical features, as the syndrome in its florid form is currently recognized, were outlined in 2006 by a Japanese consensus group by the aid of a nationwide survey in Japan [7–9]. Although there has been much debate about the criteria and considerable confusion about the name of this syndrome [7, 8, 10, 11], the clinical and histological findings reported under the name of DRESS are not significantly different from those reported under the name of DIHS. This review examines the laboratory and key clinical aspects of DIHS. Particular focus is given to the role of herpesviruses

in view of its recent inclusion in the diagnostic criteria for DIHS. Since this syndrome was last reviewed in 2007 [12], considerably more data have become available on both the immune responses involved and the long-term sequelae of the disease.

Epidemiology

DIHS is now diagnosed earlier in its clinical course than it was in the past thanks to the diagnostic criteria. According to the previous study reported by Gennis et al. [13], the incidence of DIHS is estimated to be between 1 in 1,000 and 1 in 10,000 exposures to phenytoin. However, the frequency of DIHS could be increasing, because milder forms of the disease are being recognized. The most recent and careful population-based studies in Japan report an incidence of 10 per million person-years. In Japan and EU, the incidence increases steadily with advancing age. Incidence rose sharply from 5 per million during the time between 1991 and 2000 to 10 per million between 2001 and 2009. Although DIHS has been believed to have no age and sex predilection, women are about 1.3 times more likely to be affected than are men [Kaudaun, unpubl. data] as demonstrated in patients with SJS and TEN. Our series of this syndrome showed no increased incidence of a personal or family history of atopy and drug eruptions. About half of the patients have had a flu-like illness within the previous 4 weeks, suggesting viral infections as possible triggers for this syndrome.

Clinical Findings

The disease usually starts abruptly with cutaneous lesions or fever. In some cases, there may be a prodrome with upper airway infection. The cutaneous lesions are erythematous papules and patchy erythematous macules, which may be pruritic and can become confluent. The individual lesions are often with hemorrhage and symmetrically distributed on the face, trunk and extremities. Fever usually precedes the rash by 1–2 days and temperature ranges from 38 to 40°C with spikes that may generate concern regarding an underlying infection. The most characteristic cutaneous lesions during the eariest phase of the disease are periorbital and facial edema with pinhead-sized pustules [14], simulating acute generalized exanthematous pustulosis (AGEP). Usually, patients develop these clinical symptoms more than 3 weeks after starting therapy with a limited number of drugs, as shown in table 1. A dramatic deterioration of clinical symptoms often occurs 3–4 days after withdrawal of the causative drug (fig. 1), making the diagnosis of drug eruptions most difficult. The palms and soles are usually spared, but can occasionally show a few lesions. When the causative drug continues to be given after this syndrome has developed, the eruptions often generalize into severe exfoliative dermatitis or erythroderma. Blisters are occasionally present but mainly limited to the wrists and probably related to dermal edema. Follicular

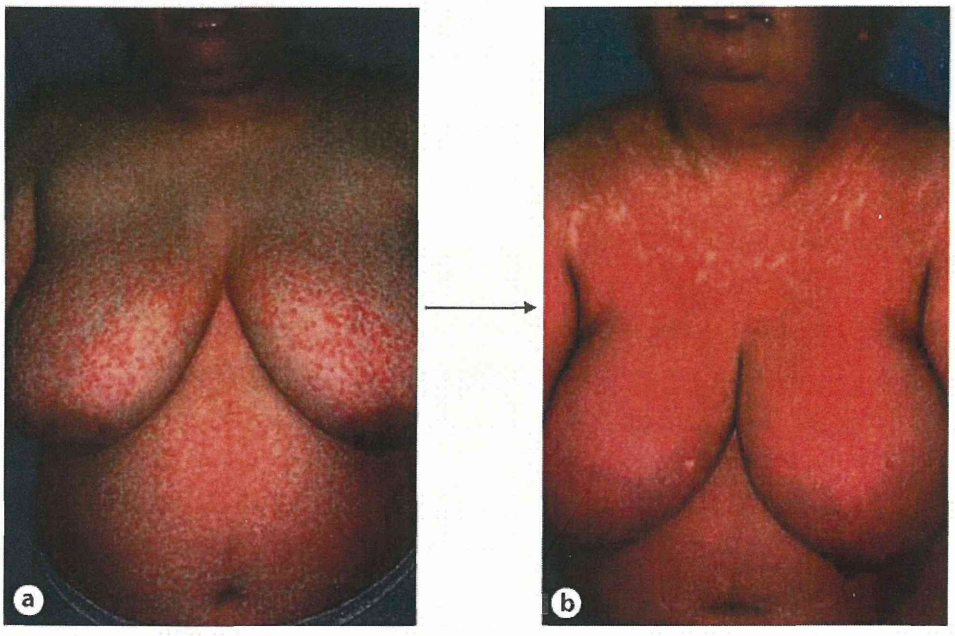

Fig. 1. The patient's clinical symptoms on the initial presentation (**a**) and 4 days after her initial presentation (**b**). A dramatic deterioration of the clinical symptoms is observed in association with an increase in body temperature despite withdrawal of the causative drug.

Table 1. Diagnostic criteria for DIHS established by a Japanese consensus group [7]

1	Maculopapular rash developing >3 weeks after starting with a limited number of drugs
2	Prolonged clinical symptoms after discontinuation of the causative drug
3	Fever (>38°C)
4	Liver abnormalities (ALT >100 U/l)[1]
5	Leukocyte abnormalities (at least one present)
	a Leukocytosis (>11 × 10^9/l)
	b Atypical lymphocytosis (>5%)
	c Eosinophilia (>1.5 × 10^9/l)
6	Lymphadenopathy
7	HHV-6 reactivation

The diagnosis is confirmed by the presence of the seven criteria above (typical DIHS) or of five of the seven (atypical DIHS).

[1] This can be replaced by other organ involvement, such as renal involvement.

accentuation of the erythematous papules is a characteristic finding of DIHS [15]. Mucosal surfaces show a few lesions, particularly lips and oral mucous membranes, more frequently than generally thought, although much less severe and hemorrhagic than SJS/TEN.

Tender lymphadenopathy can be found in >70% of patients early in the course of the illness, predominantly affecting the cervical, axillary, or inguinal nodes. Bilateral

swelling of the salivary glands with severe xerostomia can be frequently seen early in the course, suggesting that mumps virus may be reactivated before onset of this syndrome. Some patients may often complain of oral dryness which makes swallowing of dry food difficult.

Two or more internal organs are involved in many patients with DIHS. Most frequently involved organs are liver (70%) [12, 16–18], kidney (11%) [8, 12, 17, 18], and lung [18]. If hepatitis is present, it is usually anicteric [8]. Hepatomegaly accompanied by splenomegaly is a common finding. Which organs are prefentially involved is likely to be determined in part by the drug used: hepatitis is often observed in phenytoin-, minocycline-, or dapsone-induced DIHS [8, 17, 18], and kidney involvement is frequently seen in allopurinol-induced DIHS [12, 18]. Thus, various organ involvement emerges after an undefined period of critical illness of days to weeks: resolution of symptoms in one organ may be often followed by a stepwise development of other organ failures, despite withdrawal of the causative drugs. Such clinical variability in the presentation and course of clinical symptoms allows for a delay in diagnosis which may arouse suspicion of infection in doctors of first contact who may not have seen patients with DIHS. As a result, unnecessary empirical antibiotic therapy which could increase the risk of developing additional drug rashes may be started. Indeed, patients with DIHS often show unexplained cross-reactivity to multiple drugs with different structures, including those used after onset of symptoms. In some patients, to make matters worse, the fever often persists even for weeks despite discontinuation of the causative drug.

Overlap with Other Severe Drug Eruptions

Clinical and histologic observations support the view that DIHS and SJS/TEN are opposite clinical poles of a continuous spectrum of severe drug eruptions: a particular, predilection for mucosal surfaces is typically seen in SJS/TEN, but not in DIHS. More than 30% of patients with DIHS, however, also possess mucous membrane lesions, although less than those in SJS/TEN. Thus, there is considerable overlap in the clinical manifestations of both conditions. Indeed, some of our patients with DIHS had concurrent or sequential development of SJS-like mucosal and cutaneous lesions. Most of them initially presented with clinical features typical of DIHS but went on to develop SJS-like mucosal and cutaneous lesions: these patients initially present with both clinical and immunologic findings, including HHV-6 reactivation, consistent with a diagnosis of DIHS, but whose subsequent clinical pattern has evolved to become more typical of SJS/TEN. As we have recently demonstrated [19], both conditions are mediated by activated effector T (Teff) cells that can recognize drug antigen, but expansions of functional regulatory T cells are only observed in the setting of DIHS: this expansion has a proven causal relationship with the clinical symptoms and viral reactivations observed in DIHS. Thus, although the skin lesions

of both clinical entities were thought to rarely change from one clinical type to the other, it is important to understand that the conversion from DIHS to SJS/TEN is not the rare event: in many cases, SJS/TEN is usually preceded by DIHS. In these cases, occurrence of SJS-like lesions is delayed for a week after onset of clinical symptoms consistent with DIHS: this delay may be diagnostic of identifying the patients with DIHS evolving into SJS/TEN, because patients with widely distributed purpuric erythematous macules rapidly progressing into blisters and erosions over a period of a few days are likely to have SJS/TEN not associated with DIHS. Because these cases indicate that specific factors determining the expression of a particular disease phenotype may vary with time, detailed kinetic information on these patients would be helpful in determining disease expression.

Facial erythema and edema with pinhead-sized pustules as one of the relatively early symptoms of DIHS are often indistinguishable from those observed in AGEP. Clinicians who are less familiar with the clinical symptoms of DIHS and AGEP may experience the difficulties in assigning a specific diagnosis to patients presenting with facial erythema and edema associated with pustules. There is, however, considerable evidence that the two are distinct conditions with divergent clinical features. Nevertheless, the pattern of erythematous lesions in AGEP, initially with distribution around the flexural areas, is very different from DIHS where lesions usually occur on the face and upper trunk. The marked difference between the two can be also found in their disease course after withdrawal of the causative drug: spontaneous resolution of the pustules occurs in less than 15 days with characteristic desquamation [20], while DIHS usually runs a chronic unremitting course. Clearly, the clinical phenotype of severe drug eruptions varies with time and definitive diagnostic categorization is not always possible at the initial presentation.

Laboratory Findings

The peripheral blood usually shows marked leukocytosis with atypical lymphocytosis or eosinophilia of various degree. In some patients, leucopenia or lymphopenia may be seen, especially at the early stage of the illness [8, 12, 21]: this occasionally precedes leukocytosis. While eosinophilia can be seen in 60–70% of the patients in our series [8, 12], other recent studies reported that transient eosinophilia (95%) was far more frequently present [Kardaun et al., submitted] than previously reported. Occasionally, the number of monocytes is also increased, although this is a relatively late event as compared with neutrophilia and lymphocytosis, both of which can often be seen in the early stage of the disease. The increase in either CD4+ T cells or CD8+ T cells can be seen in the early phase of the disease. According to our series of 12 patients (6 male and 6 female, age range 25–70 years) with DIHS diagnosed and managed at our institution, CD4+ T-cell numbers initially increased at the early stage in >90% of these patients [22]; this increase, however, was followed by a gradual decrease reaching

normal values by 2 months after onset. In some patients, the increase in CD8+ T cell numbers was seen, although this difference was not reflected in clinical symptoms. A profound decrease in CD19+ B-cell numbers and CD56+ NK-cell numbers was observed at their initial presentation [23]. The subsequent decrease in CD4+ T cell numbers was usually coincident with improvements in clinical status. The degree of the increase in CD4+ T cell numbers best correlated with the severity of clinical symptoms, such as the extent of skin lesions and the magnitude of viral reactivations, as mentioned later.

A dramatic decrease in serum IgG, IgA, and IgM levels is typically observed at onset, and the lowest levels are usually detected a week after withdrawal of the causative drug [23]. Immediately 1–2 weeks after the nadir in their levels, the overshoot in their levels can be observed, and they eventually return to normal upon full recovery. Because these alterations in Ig levels during the course of the illness were never observed in patients with SJS/TEN and AGEP, this finding can only be diagnostic of DIHS when Ig levels are carefully measured at various points after onset. In some patients, this decrease may be only apparent when compared with those levels after full recovery, while those levels at onset may be within normal limits. Thus, it should be noted that Ig levels at a single time point are not sufficiently enough to conclude their decrease.

A marked increase in the serum alanine aminotransferase values can be seen in up to 70% of patients. In some patients, γ-glutamyl-transpeptidase, total bilirubin, and alkaline phosphatase increase to a variable degree. Such liver abnormalities often occur in association with the increase in circulating atypical lymphocytes, suggesting that activated lymphocytes may contribute to liver damage. Various forms of renal involvement have also been reported [24, 25], ranging from tubulointerstitial nephritis to granulomatous necrotizing angiitis. The mortality is likely to depend in part on the degree of renal involvement rather than hepatic involvement.

Although in earlier studies HHV-6 was thought to be the only virus that was reactivated in patients with DIHS [6], it has become clear that other herpesviruses, such as EBV, HHV-7, and CMV are also reactivated during the course of the disease [5, 26–28]. Our results of PCR analyses performed at various time points after onset showed that various herpesviruses sequentially reactivate during the course of DIHS in the order as demonstrated in graft-versus-host disease (GVHD) [27]: the cascade of reactivation events initiated by EBV or HHV-6 extends, with some delay, to HHV-7 as well, and eventually to CMV, as shown in figure 2. Our clinical observations demonstrated that reactivations of these herpesviruses can be detected coincident with the onset of various clinical symptoms, such as liver abnormalities in some patients while in other patients they occur without the evidence of overt clinical symptoms. In order to demonstrate full cascades of reactivation events during the course of DIHS, frequent sampling of blood at least on a weekly basis is needed, because the changes in viral loads are so rapid. Thus, the true peak of viral loads can easily be missed on a routine examination performed at a single time point on a routine basis.

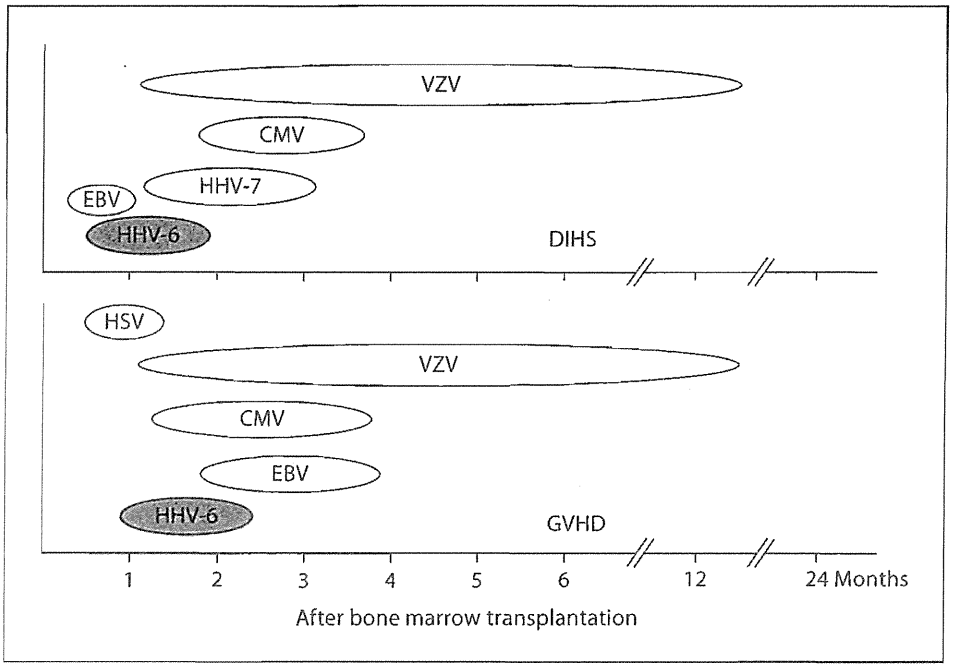

Fig. 2. The sequence of herpesvirus reactivation events observed in DIHS (upper) and GVHD (lower). Modified from our previous paper [12]. VZV = Varicella zoster virus.

Diagnosis of Drug-Induced Hypersensitivity Syndrome

The diagnosis of DIHS is usually not difficult for dermatologists who are familiar with clinical symptoms of DIHS, if a history of drug intake, particularly drugs listed in table 1, is sought in all patients presenting with fever, erythematous skin lesions predominating on the face and upper trunk, lymphoadenopathy, and other organ involvement. The diagnosis, however, can be challenging for physicians who have seen such patients before. There are a number of differential diagnostic considerations that may usually play a greater role in atypical or very early cases: they include EBV- or CMV-induced infectious mononucleosis (IM), measles, exfoliative erythroderma, a drug-induced erythrodermic condition, Kawasaki syndrome, Kikuchi-Fujimoto disease, and drug-induced pseudolymphomas. The clinical findings alone can be difficult to differentiate from IM: IM occurs most commonly in teenagers or young adults, and the eruption usually occurs 2–10 days after starting therapy with antibiotics which rarely cause DIHS, while DIHS typically occurs 3 weeks to 3 months after starting therapy with anticonvulsants in adults or elderly patients.

Although this syndrome had been recognized as a distinct disorder in the early 1960s, much of the confusion has resulted from the inconsistent and variable terminology and the lack of a specific and sensitive diagnostic test. In this regard, we and Hashimoto's group independently demonstrated that HHV-6 can be reactivated at a particular time point, 2–3 weeks after onset of rash in the vast majority of patients regardless of treatment [5, 6]. Since then, a strong association between HHV-6

Table 2. Drugs frequently causing DIHS/DRESS

• Carbamazepine	• Dapsone
• Phenytoin	• Salazosulfapyridine
• Phenobarbital	• Allopurinol
• Zonisamide	• Minocycline
• Mexiletine	• Abacavir[1]
• Lamotrigine	• Nevirapine[1]

[1] These drugs cause systemic hypersensitivity reactions with some peculiar symptoms [12].

reactivation and this syndrome has been supported by a large number of independent groups over the years in Japan. In 2006, we, a Japanese consensus group named the Japanese Research Committee on Severe Cutaneous Adverse Reaction established a set of criteria for diagnosis of this syndrome (table 2) and proposed the term 'DIHS' [7, 8]. DIHS is currently diagnosed by using the seven criteria in Japan: diagnosis of typical DIHS requires all seven criteria, although, in many cases, the criteria for DIHS are not all present on any given day. Our case series diagnosed by clinical and laboratory findings alone have shown that HHV-6 reactivation can be detected in the vast majority of patients who satisfy the other six criteria. The concept of 'atypical DIHS' can be used for patients with typical clinical presentations, in whom HHV-6 reactivation cannot be detected due to inappropriate timing of sampling or the lack of a specific test for detecting HHV-6 reactivation: the detection of HHV-6 reactivation can be evidenced by the significant rise in HHV-6 IgG titers or HHV-6 DNA levels.

Recently, an international consensus group named RegiSCAR has proposed a standardized scoring system for diagnosis [Kardaun et al., submitted], based on clinical and biological characteristics in 117 cases prospectively enrolled from 2005 to mid-2009. There is no fundamental difference in the clinical and laboratory findings except for HHV-6 reactivation between this system and our criteria, although the major concern is that, when this scoring system is used for diagnosis, the syndrome may be overdiagnosed or underdiagnosed due to the lack of a specific diagnostic test for HHV-6 reactivation. According to our experience, patients with clinical symptoms and laboratory findings consistent with those of DIHS but without the evidence of HHV-6 reactivation have shown to exhibit a tendency toward milder disease [7]. In our case series, patients who had more than two episodes of worsening after initial improvement, either treatment-related or -unrelated fluctuations, were more likely to run a chronic, unremitting course, probably due to repeated reactivations of various herpesviruses. The magnitude of HHV-6 reactivations as evidenced by the increase in HHV-6 DNA levels is thought to reflect the severity of inflammatory responses that occur in vivo in patients with DIHS. We recommend that HHV-6 testing be used to confirm a clinical diagnosis rather than simply as a screening tool.

The lymphocyte transformation test (LTT) [29] is a frequently used as a tool to confirm a clinical diagnosis of allergic drug reaction and determine the causative drug. We previously demonstrated that positive LTT reactions were obtained at the recovery stage but not the acute stage in DIHS, while in SJS/TEN and other types of drug eruptions, positive LTT reactions were only obtained when the test was performed at the acute stage [30]. Our analyses performed with the use of samples at various time points after onset showed that LTT reactions became positive from 5 weeks onward after onset in the majority of patients, regardless of whether patients were on therapy with prednisolone or not [30]. Because this finding was only observed in patients with DIHS, the LTT is a reliable method to define the causative drug in DIHS when the test is performed at the right timing. Ideally, this test should be done as soon as possible after presentation and should be repeated after 2 months. Negative LTT reactions at the acute stage could alternatively be interpreted as suggesting a diagnosis of DIHS.

Pathology

The histologic picture of DIHS is not diagnostic. The common pathological findings are superficial perivascular lymphocytic infiltrates and some extravasated erythrocytes and eosinophils. On rare occasions, DIHS may feature a lichenoid infiltrate with apoptotic keratinocytes, a finding frequently seen in other drug eruptions such as erythema multiforme type and SJS/TEN. Full-thickness epidermal necrosis and detachment can only be seen in patients with DIHS evolving into SJS/TEN. The pattern of inflammation in DIHS involves mixed infiltration composed of CD4+ and CD8+ T cells with hemorrhage. In our earlier study, high levels of HHV-6 genome and viral antigens were detected in infiltrating cells in the skin lesions taken at the early stage [5], despite the absence of HHV-6 DNA in the blood simultaneously obtained from the same patient. These results indicate that there exist other distinct, undefined compartments, such as skin, liver and lymph nodes, where herpesviruses can reactivate in sequential order independent of the blood. This may be reflected in differences in the nature of the localized immune process taking place in the target organs of DIHS.

Pathogenesis

Activated T cells seem to play an important role in DIHS, as suggested in other severe drug eruptions [19]. Previously, it was believed that DIHS merely represents an exaggerated, hyperinflammatory response with inflammation-induced viral reactivations and subsequent organ injury [9]. According to this theory, reactivations of herpesviruses specifically observed in patients with DIHS are a consequence, not a cause, of excessive activation of T cells. In this regard, we have suggested the existence of

a more complex scenario: sequential reactivations of herpesviruses would occur far earlier than onset probably due to protracted use of anticonvulsants, thereby causing the generation and activation of virus-specific memory CD8+ T cells. However, recent studies including our own have somewhat revised this theory and found that antiviral T cells can directly influence the course of DIHS and regulatory T cells confer protective immunity in this setting. In view of the fact that the clinical symptoms of DIHS remain dormant for prolonged periods after starting therapy with the causative drug, there could exist some mechanisms, whereby antiviral CD8+ T cell responses can be silenced to limit possible immunopathology before onset. If this balance mechanism is eventually disturbed, a condition is set that leads to onset of the disease. According to this scenario, memory T cells specific for a viral peptide presented in the context of certain HLA-A or -B could play a central role in the pathogenesis of DIHS, and drug antigens could serve to induce accidental activation of those virus-specific T cells with cross-reactivity to drug antigens. Consistent with this scenario, Hung et al. [31] provided evidence for a genetic predisposition in DIHS showing a strong association (100%) between allopurinol-induced DRESS and HLA-B*5801. Prospective studies of 40 patients presenting with well-characterized DRESS by Picard et al. [32] provide ample support for our scenario. They demonstrated that EBV, HHV-6, or HHV-7 reactivation can be detected in 76% of patients with DRESS and that the cutaneous and visceral symptoms of DRESS are associated with an oligoclonal expansion of activated memory CD8+ T cells that can specifically recognize one of viral antigens derived from herpesviruses. Importantly, viral replication has been shown to be enhanced by the causative drug, but not an irrelevant drug that has not been involved in the occurrence of DRESS [32]. A likely interpretation of these findings, in consideration of our own data, is that the cutaneous and visceral symptoms of DIHS can be mediated by the activation and migration into the target organ of antiviral CD8+ T cells resulting from sequential reactivation of herpesviruses.

If antiviral T cells play a central role in tissue injury, it is logical to ask by which mechanism(s) these antiviral T cells can be silenced over a prolonged period of time before onset. The most promising new insight into the protective mechanism(s) comes from the work from our group investigating the role of regulatory T (Treg) cells in patients with DIHS [19]. We have recently investigated whether Treg cell frequency and function can influence the clinical manifestations and course of DIHS. In this study, patients with TEN were also analyzed in comparison with DIHS. Dramatic expansions of fully functional CD4+CD25+FoxP3+ Treg cells were specifically found in the acute stage of DIHS [19]; in contrast, in TEN their capacity to migrate into the skin and to suppress the activation of Teff cells was profoundly impaired during the acute stage, although they are present in normal frequency in the blood. These expanded Treg cells have been shown to inhibit drug-induced cytokine production by Teff cells in vitro, indicating that the expanded Treg cells could serve to inhibit activation of antiviral T cells for a prolonged period of time before onset of DIHS, and induce sequential reactivations of herpesviruses. Our further unpublished

observations show that the causative drug can trigger the expansion of Treg cells from patients with DIHS. Our findings provide explanations for why the onset of DIHS is delayed in relation to the introduction of the causative drug, and why severe epidermal damage cannot be detected in the skin lesions of DIHS despite activation of Teff cells, why viral reactivations are induced, and why positive LTT reactions cannot be detected during the acute stage. In view of their ability to induce B cell death [33], a decrease in serum Ig levels and B cell number specifically observed during the acute stage would be explained by expansions of functional Treg cells.

Surprisingly, the Treg cells gradually lose their original suppressing function when contracted upon resolution of IDHS [19]. In contrast, a functional impairment of Treg cells during the acute stage of TEN was restored upon resolution. This progressive dysfunction of Treg cells specifically observed after resolution of DIHS could be due to their exhaustion as a consequence of repeated activation of Treg cells in response to excessive activation of Teff cells including antiviral T cells driven by a high viral load in patients.

Complications and Long-Term Sequelae

Our series of patients and a review of the English literature have suggested the following features of the natural history of DIHS. Less than 10% of patients die within 1 year after onset, and autoimmune disease or production of autoantibodies occur as a sequela of DIHS in 10% of surviving patients, regardless of whether they were treated with systemic corticosteroids. Because they appear for several months to years after the acute illness was resolved, it is difficult to find a link between preceding DIHS and the subsequent autoimmune diseases unless special attention is given to a history of a clinical illness compatible with DIHS. It should be recognized that they cannot necessarily occur immediately after resolution of DIHS but rather occur after a disease-free interval of several months to years and that there is the long prodromal period preceding clinical onset of autoimmune diseases [34]. These autoimmune diseases include type 1 diabetes mellitus [35–38], autoimmune thyroid disease [8, 12, 38], sclerodermoid GVHD-like lesions [39] and lupus erythematosus [34, 40]. In a patient who subsequently developed GVHD-like lesions, antinuclear antibody (ANA) was negative during the course of DIHS and became detectable (1:40), coincident with the development of alopecia: a dramatic increase in ANA (1:5,120) was eventually found 4 years after onset of DIHS, at her initial presentation to our Department because of sclerodermoid GVHD-like lesions, indicating that the disease process of DIHS may act as a trigger for the subsequent development of autoimmune disease [39]. Given the strong association between EBV infection and systemic lupus erythematosus (SLE) [41, 42], it is likely that EBV reactivations occurring during the episode of DIHS could profoundly influence the autoimmune sequelae of DIHS. Indeed, EBV reactivations were confirmed on two occasions, during the episode of DIHS and at

the time of the presentation with clinical manifestations of SLE in our reported case [34, 40]. In addition to the role of EBV reactivations, a gradual loss of Treg function after resolution of DIHS [19] could increase the risk of subsequently developing autoimmune disease.

Management of Drug-Induced Hypersensitivity Syndrome

Early recognition of clinical symptoms compatible with DIHS is essential in improving patient outcomes. Because paradoxical deterioration of clinical symptoms and laboratory findings is often seen 3–4 days after withdrawal of the causative drug, a concern of an underlying infection may be generated; and, as a result, empirical treatment with antibiotics or nonsteroidal anti-inflammatory drugs may be initiated, which often confuse or worsen the clinical picture probably due to unexplained cross-reactivity to these drugs. The use of those drugs should be avoided, particularly during the acute phase.

Systemic corticosteroids is the mainstay of treatment, particularly in the earlier stages of the disease. Rapid resolution of rashes and fever occurs within several days after starting a moderate dose of systemic corticosteroids (prednisolone, 40–50 mg/day). Because marked deterioration of various clinical symptoms is frequently seen with abrupt discontinuation or rapid tapering of corticosteroids, corticosteroid dose should be reduced gradually even upon resolution of clinical manifestation: tapering corticosteroids more gradually over a prolonged period of time (usually 6–8 weeks) can help to limit the severe flare-ups. One should recognize that patients with DIHS are at greater risk of subsequently developing the wide spectrum of immune reconstitution syndrome (IRS) ranging from CMV disease to autoimmune disease [8, 12, 22, 34] (table 3), and the use of systemic corticosteroids represents an important factor that increases the risk of disease progression to full manifestations of IRS upon the withdrawal or reductions. Indeed, HHV-6 and CMV, but not EBV, viral loads were significantly higher in patients with DIHS receiving systemic corticosteroids compared with those without corticosteroid therapy [Ishida et al., submitted]. This finding indicates that the degree and duration of HHV-6 and CMV reactivations would be greatly influenced by the use of immunosuppressive drugs. Nevertheless, this effect of corticosteroids on viral reactivations is likely to be an unanticipated consequence of a tapering corticosteroid dose, because our frequent monitoring of viral loads in patient with DIHS revealed that the increase in CMV viral loads coincided with a tapering of corticosteroid dose [43]. Given the high risk of sequelae from CMV reactivation in patients with DIHS [43], the direct anti-CMV medications with a gradual reducing dose of corticosteroids may help to avoid disease progression to full manifestations of IRS [22].

The use of intravenous immunoglobulin (IVIG) has so far only been assessed in some patients; however, our trials of combining treatments, giving IVIG (0.1 g/kg per

Table 3. Reported clinical illness consistent with IRS in HIV-negative hosts [22]

Mycobacterium avium complex infection
Tuberculosis
Cryptococcosis[1]
Herpes simplex[1]
Herpes zoster[1]
Hepatitis C virus
Hepatitis B virus
CMV[1]
Kaposi sarcoma
Sarcoidosis
Graves' disease
Hashimoto thyroiditis[1]
DIHS

[1] Infectious and autoimmune diseases often observed during the course of DIHS or long after its resolution.

day for 3 days) together with systemic corticosteroids, have failed to show extra benefit compared with corticosteroids alone. Because patients with moderate disease can often recover from this syndrome by supportive care without the need of systemic corticosteroids within 3 weeks, the use of systemic corticosteroids is not necessarily recommended as a treatment option of DIHS. Particularly, a small dose (prednisolone, 10–20 mg/day) of systemic corticosteroids followed by small increments in dosage at short intervals should be avoided even for mild cases, because this may not be sufficient to ameliorate clinical symptoms and may result in unnecessarily protracted use of corticosteroids. Thus, although systemic corticosteroids have become accepted as the gold standard treatment for DIHS, it remains to be determined whether treatment with systemic corticosteroids is also beneficial from a viewpoint of disease outcome and sequleae. Nevertheless, the benefit is greatest during the first 2–3 weeks when treatment was given early. Likewise, there was also no significant improvement in patients treated with corticosteroids for other important outcomes including time to discharge, death and disability after 1 year. Our longitudinal PCR analyses of viral loads in patients with DIHS justify the frequent monitoring of viral reactivations to predict and improve the short-term or long-term outcome.

Conclusion

The development of an internationally standardized scoring system to clearly identify patients with DIHS will be critical in treating those who had suffered from preventable

morbidity and mortality. Considerations for the development of therapies that can reduce the risk of long-term sequelae such as autoimmune disease would seem a reasonable path to pursue.

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