Current Concepts on the Diagnosis and Pathogenesis of Drug-induced Hypersensitivity Syndrome

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Abstract
Drug-induced hypersensitivity syndrome (DIHS) is a life-threatening, multi-organ system reaction. The clinical picture of this syndrome is highly variable and not so distinctive that the diagnosis can be made on clinical grounds; this syndrome is often missed in the differential diagnosis of patients presenting with fever, rash, and lymphadenopathy, probably due to a lack of awareness. This syndrome has several unique features: they include the delayed onset, paradoxical deterioration of clinical symptoms after withdrawal of the causative drug, and unexplained cross-reactivity to unrelated multiple drugs. These features cannot be solely explained by drug etiology. We have demonstrated that human herpesvirus 6 (HHV-6) can be specifically reactived 2–3 weeks after the onset and the test for detecting HHV-6 reactivation has become the gold standard test for identifying patients with DIHS. This review briefly discusses many of the important changes that explain the diversity of the clinical symptoms of DIHS.

Key words Drug-induced hypersensitivity syndrome (DIHS), Human herpesvirus 6 (HHV-6), Regulatory T cells, Viral infection, Anticonvulsants, Autoimmune sequelae

Introduction
Despite intense efforts, severe drug eruptions remain a serious clinical problem with significant morbidity and mortality and are considered one of the most important global heath problems. There are estimated thousands deaths due to severe drug eruptions each year worldwide. Although underlying viral infections have been suggested to increase infected patients’ susceptibility to severe drug eruptions, the relationship between viral infections and the development of severe drug eruptions has not been extensively explored until recently. There is an accumulating body of clinical evidence, however, that suggests that some herpesviruses may contribute to the pathogenesis of specific subgroup of severe drug eruptions. This narrative review focuses on the key clinical aspects of this subgroup of severe drug eruptions, which had been described under different names. Particular focus is given to viral reactivations in view of their recent inclusion in the diagnostic criteria of this subgroup.

Diagnosis
This disorder was initially described by Chaiken et al.1 in 1950: they reported a patient who had developed rash associated with lymphadenopathy and multiorgan failure long after stating an aromatic anticonvulsant drug. Since then there have been many case reports describing similar reactions to other anticonvulsant drugs, such as phenytoin, phenobarbital, and carbamazepine. In 1988, Shear and Spielberg2 coined the term ‘anti-convulsant hypersensitivity syndrome’ to refer to
Roujeau et al. introduced the term ‘drug reaction with eosinophilia and systemic symptoms (DRESS)’ for this disorder to encompass these diverse clinical presentations. Although this syndrome was 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, my group and Hashimoto’s group independently demonstrated that human herpesvirus 6 (HHV-6) can be reactivated at a particular time point, namely 2–3 weeks after the onset of rash in the vast majority of patients with this syndrome, despite the diverse clinical presentations at onset: the detection of HHV-6 reactivation was evidenced by the rise in HHV-6 IgG titers or HHV-6 DNA levels. Because this reactivation was commonly observed 2–3 weeks after the onset regardless of treatment in the Japanese patients with this syndrome so far reported (Fig. 1), the detection of HHV-6 reactivation has become a requisite laboratory feature for the diagnosis to be made.

Table 1 Diagnostic criteria for DIHS established by a Japanese consensus group

1. Maculopapular rash developed >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 >100U/L)*
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).
* This can be replaced by other organ involvement, such as renal involvement.

Work undertaken by a number of independent groups over the years, ours included, in defining the clinical features of this syndrome has supported a strong association between HHV-6 reactivation and this syndrome.

In 2006, we, a Japanese consensus group named the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR), established a set of criteria for diagnosis of this syndrome (Table 1) and proposed that the
term ‘drug-induced hypersensitivity syndrome (DIHS) be used instead of DRESS to avoid confusion’; this is because eosinophilis is seen at most in 60–70% of patients who satisfy the criteria. There have been no significant differences in the clinical findings of patients with DIHS reported based on the criteria and those reported under the name of DRESS, although the latter includes patients with a tendency toward milder disease. Thus, DIHS is currently diagnosed by use of the seven criteria in Japan: diagnosis of typical DIHS requires all severe criteria. Our case series diagnosed by clinical and laboratory findings alone have shown that HHV-6 reactivation can be detected in the vast majority (>95%) 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. In many cases, the clinical criteria for DIHS are not necessarily all present on any given day, particularly at onset.

**Clinical Findings**

This syndrome typically occurs with fever or cutaneous lesions 3 weeks to 3 months after starting therapy with a limited number of drugs, mainly anticonvulsant drugs (Table 2). The delayed onset in relation to the introduction of the causative drug is one of the unique features of DIHS that can be distinguished from other types of drug eruptions, which usually start 1–2 weeks after starting therapy. The maculopapular or erythematous eruptions are initially observed on the face (Fig. 2), upper trunk (Fig. 3) and upper extremities: one of the characteristic features of the eruption at the early stage is periorbital, facial, or neck erythema and edema studded with pinhead-sized pustules. Although some erythematous macules may coalesce to form blisters, most of the erythematous macules do not evolve into blisters and no mucous membrane involvement is usually seen. The paradoxical worsening of clinical symptoms often occurs 3–4 days after withdrawal of the causative drug (Fig. 2B) and is also characteristic of DIHS. Interestingly, patients with DIHS often show unexplained cross-reactivity to multiple drugs with different structures, including to those used after the onset of symptoms. Liver abnormalities occur in up to 70% of patients while various forms of renal

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<th>Drugs frequently causing DIHS / DRESS</th>
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<td>Carbamazepine</td>
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Fig. 2  A: The patient’s face on initial presentation shows slight erythema.  B: The patient’s face on admission 3 days after his initial presentation showed edema, erythema studded with small pustules, and lymphadema despite discontinuation of the causative drug.

Fig. 3  The patient’s chest and abdomen showed confluent purpuric erythematous rash on admission, 3 days after discontinuation of the causative drug.
involvement have also been reported.\(^6\) The mortality from DIHS can be approximately 10% in our case series and has been correlated with the degree of renal involvement rather than hepatic involvement. In many severe cases, these symptoms continue to deteriorate or several flare-ups can be seen even for weeks after withdrawal of the causative drug; resolution of symptoms in one organ is often followed by a step-wise development of other organ system failure.

**Laboratory Findings**

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.\(^8\) Immediately 1 to 2 weeks after the nadir in the decrease, the overshoot in Ig levels is transiently observed and they finally return to normal upon full recovery (Fig. 1).

Because in the earlier studies HHV-6 was the only virus that was found to be reactivated in patients with DIHS,\(^4,5\) reactivation of HHV-6 was implicated in the pathogenesis of DIHS. Recent studies have demonstrated, however, that other herpesviruses, such as Epstein Barr virus (EBV), HHV-7, or cytomegalovirus (CMV) are also reactivated during the course of the disease\(^9\); our real-time PCR analyses of viral loads in blood samples obtained at various time points from patients with DIHS showed that the cascade of reactivation events initiated by HHV-6 or EBV extends, with some delay, to HHV-7 as well, and eventually to CMV (Fig. 4). Interestingly, this cascade of sequential herpesvirus reactivation observed in DIHS is similar to that observed in graft versus host disease (GVHD).\(^9\) Our clinical studies demonstrated that reactivations of these herpesviruses can be detected coincident with the onset of various clinical symptoms in some patients while they are not associated with the evidence of overt clinical symptoms in other patients. Thus, frequent deterioration or several flare ups occurring despite discontinuation of the causative drug could be explained in part by sequential reactivations of these herpesviruses.

**Sequelaes of DIHS: Involvement of regulator T cells**

Although various clinical symptoms develop at various time points after withdrawal of the causative drug, the resolution of these clinical symptoms eventually occurs after undefined periods of time (months). Several months to years after the acute illness was resolved, however, several autoimmune diseases have been reported to occur.

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**Fig. 4** The sequence of herpesvirus reactivation events observed in DIHS and GVHD\(^7\)
as sequelae of DIHS\textsuperscript{10–13}: they include type 1 diabetes mellitus, autoimmune hypothyroidism, and systemic lupus erythematosus (SLE). Because they may often occur after an interval of many years, it is difficult to find a link between DIHS and the subsequent autoimmune diseases unless special attention is given to the occurrence.

Activated T cells seem to play an important role in DIHS, as suggested in other severe drug eruptions. Previously, it was believed that DIHS merely represented an exaggerated, hyperinflammatory response with inflammation-induced viral reactivations and subsequent organ injury. More recent data indicate that there is substantial heterogeneity in patients’ inflammatory responses with the early stage representing immuno-suppressed as evidenced by a decrease in serum Ig levels, whereas the late stage after clinical resolution represents immuno-stimulated: patients with DIHS often develop autoimmune diseases after resolution, as described later. Indeed, DIHS is unique in that the severe epidermal damage seen in other severe drug eruptions, such as toxic epidermal necrolysis (TEN), is absent, sequential reactivations of herpesviruses occur, and autoimmunity often ensues. The most promising new insight into the pathogenesis comes from our own work investigating the role of regulatory T (Treg) cells in patients with DIHS. We have recently investigated whether changes in Treg cell frequency and function contribute to variability in the clinical manifestations of DIHS and explain various unique features of DIHS.\textsuperscript{14} To this end, we examined the frequency, phenotype and function of Treg cells both during the acute stage and again long after the clinical resolution of DIHS. In this study, patients with TEN, another end of the spectrum of severe drug eruptions, were also analyzed in comparison with DIHS. Dramatic expansions of functional Treg cells were found in the acute stage of DIHS\textsuperscript{14}. In contrast, in TEN their capacity to migrate into the skin and to suppress the activation of effector T cells was profoundly impaired although they can be present in normal frequencies in the blood. This expanded Treg cells would limit the severity of a T cell-mediated immunoinflammatory response to the drug. These findings provide an explanation for why severe epidermal damage cannot be detected in the skin lesions of DIHS, unlike TEN lesions, why the onset of DIHS is delayed in relation to the introduction of the causative drug, and why proliferation of drug-specific T cells as evidenced by lymphocyte transformation tests (LTT) can only be detected at the resolution stage of DIHS, but not at the acute stage.\textsuperscript{15} Because Treg cells have been shown to have the ability to induce B cell death,\textsuperscript{16} a decrease in serum Ig levels specifically observed at the onset of DIHS may be related to expansions of functional Treg cells. Surprisingly, Treg cells contracted upon the resolution of DIHS became functionally deficient.\textsuperscript{14} A gradual loss of Treg function after the resolution of DIHS may increase the risk of subsequently developing autoimmune diseases.\textsuperscript{13} In contrast, Treg function was profoundly impaired in the acute stage of TEN but their functional defects were restored upon resolution.

Conclusion

Although great strides have been made in our understanding of the pathogenesis of DIHS,\textsuperscript{6,7,13,17,18} several important questions remain unanswered. They include the following: 1) What is the precise role of viral reactivations in the organ injury? 2) Is there an efficient treatment that can be used to reduce the risk of subsequently developing autoimmune diseases? 3) Why are Treg cells specifically expanded at the acute stage of DIHS? 4) How do Treg cells lose their functional activity upon the clinical resolution of DIHS? Thus, the relevant future research agenda is multifaceted. First of all, it should be emphasized that the prevalence of DIHS in Japan have decreased remarkably with the spread of knowledge on DIHS associated with the increase in the availability of a specific diagnostic test to detect HHV-6 reactivation: until the specific diagnostic test was devised, many patients with clinical symptoms consistent with DIHS had been misdiagnosed and suffered preventable morbidity and mortality. For physicians in other countries, priorities should focus on the increase in the availability of the diagnostic test, so that all patients who need treatment can be identified. Secondly, the development of novel assays that can simultaneously detect reactivations of various herpesviruses and their subsequent validation will be of great utility. Thirdly, considerations for the development of therapies that can reduce the risk of subsequently developing autoimmune diseases in patients with DIHS would seem a reasonable path to pursue.
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References