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.

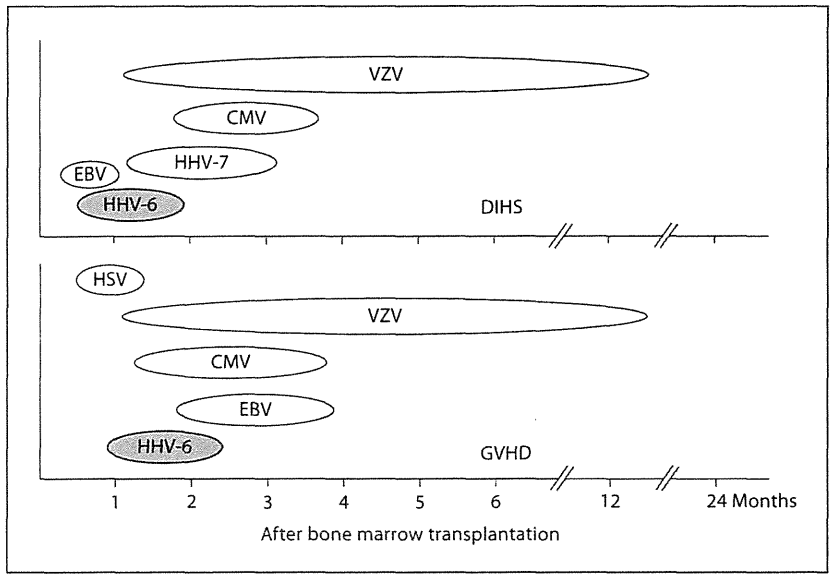

Fig. 2. The sequence of herpesvirus reactivation events observed in DIHS (upper) and GVHD (lower). Modified from our previous paper [12]. VZV = Varicella zoster virus.

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.

Acknowledgement

This work was supported in part by grants from the Ministry of Education, Culture, Sports, Science and Technology (to T.S.) and the Health and Labour Sciences Research Grants (Research on Intractable Diseases) from the Ministry of Health, Labour and Welfare of Japan (to T.S.).

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Dr. Tetsuo Shiohara
Department of Dermatology, Kyorin University School of Medicine
6-20-2 Shinkawa, Mitaka
Tokyo 181-8611 (Japan)
Tel. +81 422 47 5511, E-Mail tpshio@ks.kyorin-u.ac.jp

French LE (ed): Adverse Cutaneous Drug Eruptions.
Chem Immunol Allergy. Basel, Karger, 2012, vol 97, pp 106–121

Fixed Drug Eruption: The Dark Side of Activation of Intraepidermal CD8+ T Cells Uniquely Specialized to Mediate Protective Immunity

Tetsuo Shiohara · Yoshiko Mizukawa

Department of Dermatology, Kyorin University School of Medicine, Tokyo, Japan

Abstract

Fixed drug eruption (FDE) is generally regarded as representing the mild end of drug-induced dermatitis, but the clinical importance of recognizing this disease as an abortive, localized variant of toxic epidermal necrolysis has received increasing attention in recent years. FDE often presents with a wide spectrum of clinical manifestations indistinguishable from those of other skin diseases, such as erythema multiforme, Stevens-Johnson syndrome /toxic epidermal necrolysis, cellulitis, paronychia, lichen planus, and parapsoriasis en plaques. These unusual forms of FDE are likely to be overlooked unless the possibility of a drug etiology is routinely considered in the differential diagnosis of any patient with these diseases. Clinical awareness and recognition of these unique forms are essential for avoiding a misdiagnosis. Intraepidermal CD8+ T cells resident in the FDE lesions that have the capacity to rapidly produce large amounts of IFN-γ are likely to have a key role in mediating localized epidermal injury, while they may represent a T cell subset uniquely specialized to mediate protective immunity against various pathogens.

Essentials in a Nutshell

- Fixed drug eruption (FDE) is a relatively common dermatitis
- Classic FDE is characterized by a solitary or small number of well-circumscribed, round and/or oval erythematous macules and plaques with dusky centers on the skin and/or mucous membrane which tend to recur at exactly the same site with each administration of the causative drug ('recall' or 'isotopic' phenomenon)
- FDE typically resolves after discontinuation of the causative drug, leaving hyperpigmentation at the site of lesions

- A nonpigmenting, multiple variant of FDE that closely resembles toxic epidermal necrolysis (TEN)/Stevens-Johnson syndrome (SJS) clinically is a diagnostic challenge, is often associated with systemic symptoms, and should be considered as a severe adverse cutaneous drug eruption
- Although the most frequently implicated medications are antibacterial agents and nonsteroidal anti-inflammatory drugs, the causative drugs differ from country to country
- FDE is mediated by skin-resident CD8+ T cells of the effector memory phenotype with the capacity to specifically recognize drug antigen

Introduction

FDE is a relatively common dermatitis, affecting individuals from childhood to adulthood of all ethnic backgrounds throughout the world, although susceptibility appears to be shaped by genetic influences [1]. Although the most frequently implicated medications are antibacterial agents and nonsteroidal anti-inflammatory drugs [2], the causative drugs differ from country to country and follow the local patterns of drug usage; thus, the number of cases of FDE caused by a particular drug is largely influenced by the amount of that drug taken nationwide, either on prescription or after purchase over the counter, in addition to its intrinsic ability to cause an FDE [3]. The traditional view of the pathogenesis is that localized cutaneous inflammation observed in FDE is mediated by T cells migrating from the circulation, with the capacity to specifically recognize drug antigen, like other drug eruptions. In the late 1990s, we demonstrated that FDE cases were associated with intraepidermal T cells originally resident in the lesional epidermis [4–7], validating the concept that FDE is mediated by such skin-resident T cells with overly aggressive activity of the effector memory phenotype which, on the other hand, preserve protective functions against pathogens [2, 4–7].

In recent years, attention has also been focused on the clinical and histological resemblance of the nonpigmenting, multiple variant to TEN, the most severe drug eruption. Although FDE is generally regarded as representing the mild end of drug-induced dermatitis, the clinical importance of recognizing this disease as an abortive, localized variant of TEN has received increasing attention over the last 5 years [8]. In addition, because a recall phenomenon or isotopic response can be typically seen in FDE lesions [9], this disease may also serve as an important clue in understanding the pathomechanism of a recall phenomenon [10]. Because the clinical spectrum of FDE is highly variable, contrary to the widely held belief, in this review we would also like to expand on the clinical and histopathologic spectrum of FDE by describing patients with unusual clinical features. The wide spectrum of clinical manifestations may highlight the complex role of skin-resident T cells in various cellular mechanisms.

Thus, we review these and other recent studies and their implications for our understanding of FDE.

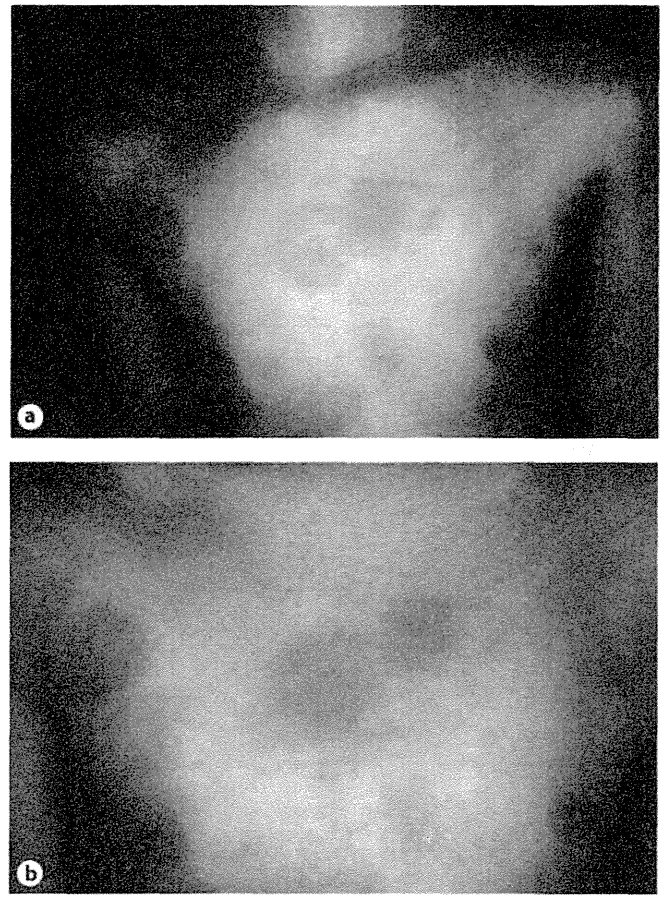

Fig. 1. **a** Typical multiple FDE lesions. Several round to oval, dusky red macules and plaques on the trunk 20 min after clinical challenge with the causative drug. **b** One h after clinical challenge, erythematous macules and plaques developed on most of the previously involved areas.

Clinical Manifestations of Fixed Drug Eruption

Clinical manifestations of FDE are not as straightforward as textbooks sometimes indicate and, as a result, FDE is undoubtedly underdiagnosed. The classic FDE lesions are characterized by a solitary or small number of well-circumscribed, round and/or oval erythematous macules and plaques with dusky centers on the skin (fig. 1) and/or mucous membrane; these lesions usually start abruptly at exactly the same site with each administration of the causative drug. The appearance of these lesions is often preceded and/or accompanied by sensation of itching or burning. These lesions typically resolve after discontinuation of the causative drug, leaving hyperpigmentation at the site of lesions. Therefore, the diagnosis of FDE is thought to be easy for many dermatologists even after clinical resolution, when these lesions are single or more round or oval demarcated hyperpigmented lesions. The individual lesions are 1–4 cm in diameter and rarely exceed 10 cm. The lesions usually appear within 30 min to 8 h after drug intake: mean length of time from drug intake to the onset of symptoms is

approximately 2 h [11]. These FDE lesions become more numerous and more severe unless the causative drug is withdrawn. New FDE lesions often occur at the site of previously traumatized or inflamed skin such as insect bites, burn, and venepuncture sites [12]. Although FDE lesions occur anywhere on the skin or mucous or genital membranes, the most commonly affected locations are the lip, palms, soles, glans penis, and groin areas. Some FDE lesions evolve into bullous and generalized eruptions mimicking SJS and TEN. After discontinuation of the causative drug, these FDE lesions spontaneously resolve over several days, a finding that cannot be observed in severe drug eruptions such as SJS and TEN, in which lesions continue to increase in size and number several days after withdrawal of the causative drug.

Although systemic manifestations are usually absent in cases with typical FDE lesions, multiple lesions are often associated with systemic manifestations including malaise, high fever, nausea, and arthralgia [2, 5, 8, 13]. Because blister formation often occurs at an advanced stage in these patients, it is difficult to distinguish between TEN/SJS and such a multiple variant of FDE, particularly when the bullous lesions become more widespread in association with systemic manifestations and do not leave typical hyperpigmentation. In 1987, Shelley and Shelley coined the term nonpigmenting FDE (NPFDE) to refer to this variant [14]. Because the clinical features of such a nonpigmenting, multiple variant closely resemble those of TEN/SJS, this variant is frequently misdiagnosed as TEN/SJS unless dermatologists take special care to recognize the presence of this entity: this variant will be described later. The shade of the hyperpigmentation tends to become darker with each succeeding exacerbation. This tendency is more prominent in dark-skinned patients, such as Asians, while in light-skinned patients, such as Caucasians, the color of such lesions remains purplish gray to slate gray even after numerous episodes [15], making it difficult to identify the lesion as being 'fixed'. For this reason, FDE in light-skinned patients is easily misdiagnosed with erythema multiforme (EM) and inflammatory skin diseases.

Most FDE lesions occur with orally administered rather than injected drugs: the most common causative drugs are pseudoephedrine, trimethoprim, tetracycline, barbiturates, sulfonamide, mefenamic acid, acetylsalicylic acid, phenolphthalein, ibuprofen, and oxyphenbutazone. Over-the-counter drugs containing several medications often cause FDE. In some patients, FDE lesions can occur after sexual intercourse or kissing with their partners taking the offending drugs [16]: the lesions on the penis and the lip that were probably caused by contact with drugs seemingly present in the vaginal fluid and the oral cavity, respectively.

Although the incidence of FDE is generally thought to be decreasing, particularly in the Western world with a much lower usage of medications causing the FDE, the unusual form of FDE described later is likely to be increasing probably due to unawareness of the unusual presentation. Following each exacerbation, some FDE lesions fail to recur despite administration of the causative drug, which is known as the refractory period [7]. The duration of this period is variable, lasting from a few weeks to several months. Guin et al. [17] reported that the FDE lesions appeared to

wander because some of the previously involved sites did not flare with each exposure while others flared: this peculiar eruption would be caused by a prolonged refractory period and the tendency to become completely refractory in some lesions, but not in others. Because of this period, in some patients there may be a delay of several weeks between drug intake and the development of FDE lesions.

FDE lesions can be reproduced upon administration of related drug/agents with chemical structures similar to the inducing offending drug, which is referred to as cross-reactivity. In some patients, however, drug/agents with totally different chemical structures can activate the FDE lesions at exactly the same sites as did the inducing offending drug, a phenomenon known as polysensitivity [18]. Polysensitivity is much more common than is actually reported and may have been overlooked in the past because of the relatively low recognition of this phenomenon.

In some patients, the FDE lesions can only be reproduced when multiple drugs are administered in combination but not separately [19]. Whatever the precise mechanism of action of the combination in causing the FDE lesions, combined stimulation by multiple drugs with unique immunomodulatory properties may be needed for precipitating exacerbations.

There have been many reports describing patients with typical FDE lesions but who had no significant history of drug intake preceding the eruption. Some of such cases of recurrent exacerbations of the FDE lesions without significant history of drug intake might be attributable to several nonspecific exogenous factors. Indeed, nonmedical factors, such as food, dermographism, and ultraviolet irradiation, have been reported to precipitate exacerbations of FDE lesions [20–24]. The FDE lesions precipitated by the ingestion of a particular food can be termed fixed food eruption [20–22], although it is unclear whether the triggering agents that originally induced the lesions were indeed drugs in these cases.

Despite the continued administration of the causative drug, the spontaneous resolution of FDE lesions has been known to occur in some patients, indicating that these patients would be spontaneously desensitized to the causative drug. Indeed, Kelso and Keating [25] reported successful desensitization for treatment of FDE to allopurinol.

Unusual Forms of Fixed Drug Eruption

FDE shows varying clinical and histologic expressions: very unusual forms including NPFDE have been reported. NPFDE is such a variant often associated with systemic manifestations, such as malaise, high fever, nausea, and arthralgia and represents the most extensive form of FDE. According to the original description by Shelley and Shelley [14], multiple, large, erythematous, well-circumscribed plaques are symmetrically located in the axillae, groins, pubis, flanks, and intergluteal fold (fig. 2). Although a classic form of pigmented FDE (PFDE) is generally recognized as representing the mild end of drug-induced reactions, generalized bullous NPFDE may

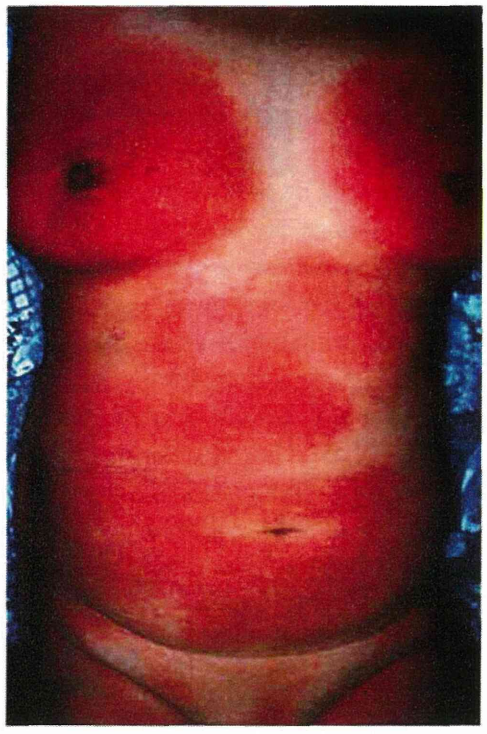

Fig. 2. Typical NPFDE lesions. Large, round to oval, erythematous plaques can be seen on the trunk. These lesions cleared without leaving pigmentary changes.

represent the severe end of FDE: it remains to be determined, however, whether this variant is a severe form of FDE or an abortive variant of the TEN spectrum [8]. In generalized bullous NPFDE, bullous lesions often continue to increase in number and may evolve into TEN/SJS-like lesions unless the causative drug is withdrawn. In this regard, some authors have argued that TEN/SJS may be a severe form of bullous FDE. At least, it should be recognized that, in many cases, TEN/SJS is defined empirically by its typical clinical and pathologic features without the confirmation of the causative agents, because of its clinical severity. The differential diagnosis of NPFDE includes bullous pemphigoid when large bullae appear on the involved areas.

NPFDE has been reported to develop in patients after general anesthesia [26]: because this reaction after the anesthesia is not generally recognized and it develops several hours after the anesthesia, it is difficult to note the link between drug administration and the appearance of a peculiar and rare type of the eruption. During the anesthesia, a variety of drugs able to be incriminated as the causative drug of FDE, such as codeine, morphine, opium, and barbiturates, are used. In this case, when anesthesia was induced with menthohexital sodium instead of thiopental, the patient had no reaction, suggesting a link between thiopental and appearance of the NPFDE lesions.

A peculiar linear pattern of FDE lesions have been also reported, although it is unclear whether the patient had preceding herpes zoster before onset of FDE [27]. Because the linear erythema occurred along the dermatomes suggesting a zoster sine

herpete episode, this linear type of FDE may be caused by immune responses to herpes zoster previously unrecognized although triggered by the drug.

An unusual cellulitis-like FDE due to topotecan has also been reported [28]: an erythematous and edematous plaque with undermined borders mimicking cellulitis was elicited by the subsequent administration of the offending drug at the same sites, confirming the diagnosis of FDE. These findings suggest that FDE lesions can be reproduced at exactly the same sites of previously damaged skin by various exogenous stimuli, such as varicella-zoster virus [27] and previous cellulitis [28], or paronychia [29]. In these cases, not only the site but also the shape of the original disease can be reproduced in the FDE lesions. In this regard, we proposed the concept of trauma-localized FDE [10]: FDE lesions initially appeared at exactly the same sites of a previous trauma, such as burn scars and insect bites, and at venipuncture sites. This concept is helpful for our understanding of the mechanism of FDE and other inflammatory skin diseases such as lichen planus, which often appear in their particular areas of prediction, a finding known as 'recall phenomenon' [30, 31].

Another unique type of FDE shows multiple, chronic, superficial lesions persisting unchanged for several months [32]. The clinical picture nearly resembled parapsoriasis en plaques. In view of the fact that FDE has generally been regarded as an acutely inflamed skin disease, this chronic type of FDE is exceptional and may be easily overlooked. The diagnosis of the chronic type of FDE was made on the basis of prompt resolution upon withdrawal of the causative drug and the reproducibility of the eruption by administration of the drug: because in this case the patient took acetaminophen many times daily, this may have contributed to the chronic nature of the condition. In contrast, the classic 'acute' type of FDE would be induced by intermittently administered drug: on the other hand, the continued administration of the causative drug may result in desensitization to the drug.

Because FDE lesions of unusual forms as described above can be easily overlooked without a detailed history of drug intake and careful examination of the lesions, such cases may be at greater risk for repeated episodes of exacerbations by drug intake. Thus, the possible sequence of progressive exacerbation on repeated administration of the causative drug can mimic a variety of idiopathic skin diseases including EM, parapsoriasis, and mycosis fungoides [33]. The diagnosis of FDE is likely to be missed unless the possibility of a drug etiology is routinely considered in the differential diagnosis of patients with these diseases. The consequences of not diagnosing FDE or misdiagnosing these diseases could be devastating, because most of the improvement is seen over the first week after withdrawal of the causative drug: however, unless a search is made to identify a relevant causative drug, and exposure to the drug is avoided, repeated administration of the causative drug would result in progressive and irreversible disease. Keeping these considerations in mind, the spectrum of FDE has recently been expanded to include cases with such unusual clinical presentations. Clinical awareness and recognition of these unique features are essential for avoiding misdiagnosis.

Histology of Fixed Drug Eruption

The histologic picture of FDE is the prototype of a lichenoid tissue reaction [2, 5, 34] with melanin incontinence: the major changes are hydropic degeneration of basal keratinocytes associated with lymphocytic invasion of the epidermis involving mainly the interfollicular epidermis. These changes are typically observed in the FDE lesions on day 1 to 2 after administration of the causative drug, at which time most biopsy specimens are obtained. In interpreting these findings in FDE lesions at a given time, however, one must appreciate the fact that biopsy specimens obtained for diagnostic purposes represent a single time point in the evolving FDE lesions. The dynamics of evolving FDE lesions have unfortunately not been adequately investigated in the past. We therefore obtained biopsy specimens from virtually the same site after rechallenging patients with the causative drug, to follow the orchestrated series of events resulting in epidermal injury from the beginning [5, 8, 13]. The results showed remarkable differences depending on the time after rechallenging and the site biopsied.

Before rechallenge, a small number of lymphocytes were aligned along the epidermal side of the dermoepidermal junction and minimal perivascular lymphocytic infiltrates were detected: the epidermis appeared normal except for the presence of lymphocytes. At 2–3 h after rechallenge, when irritation and slight erythema appeared in the previously involved sites, lymphoid cells originally adhering to the basal layer moved upward to the lower half of the epidermis, while preserving the epidermal architectures. Neither hydropic degeneration of the basal layer nor an extensive exocytosis of lymphoid cells in the epidermis was seen at this time. Typical changes in FDE lesions consisting of hydropic degeneration of the basal layer and the extensive exocytosis of lymphoid cells were seen at 24–48 h. The extent of epidermal damage seen at the peak in FDE lesions is highly variable depending on the lesion examined, ranging from confluent epidermal necrosis resembling TEN to spongiotic epidermis. Thus, confluent epidermal necrosis, said to be specific for TEN but not in FDE, can be occasionally seen in FDE lesions and is largely a function of the site of lesions biopsied. Melanophages were abundantly detected in the upper dermis of classic PFDE lesions at any stage of lesions. In contrast, a few if any melanophages were present in NPFDE lesions, consistent with the lack of hyperpigmentation. Severe epidermal damage, however, can be also detected in some NPFDE lesions, not consistent with the original description by Shelley and Shelley [14], who proposed that the drug-induced immune responses in NPFDE are primarily directed against the dermis and spare the epidermis. Nevertheless, our finding can be reconciled with the severe nature of the clinical presentations of the NPFDE.

Although inflammatory cellular infiltrates observed at the peak of FDE lesions are predominantly composed of lymphoid cells, a mixed cellular infiltrate made up predominantly of neutrophils, nuclear dust, eosinophils and lymphohistiocytic cells can be also seen in some FDE lesions. FDE with the histopathological findings of a neutrophilic dermatosis has also been reported. Agnew and Liver [35] described this