Osteonecrosis of the Femoral Head in a Patient with Henoch-Schönlein Purpura and Drug-induced Hypersensitivity Syndrome Treated with Corticosteroids

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Osteonecrosis of the femoral head (OFH) is a progressive, debilitating disease that commonly leads to destruction of the hip joint. Most patients with OFH require surgery within a few years of onset (1). It has been shown that a variety of collagen diseases, such as systemic lupus erythematosus (SLE) and systemic vasculitis, are involved in the occurrence of non-traumatic OFH (2–5). Numerous reports have documented OFH after oral corticosteroid treatment. However, it is uncertain if corticosteroid treatment alone or in combination with other factors leads to the occurrence of OFH. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a severe drug reaction with multiple organ involvement (6, 7). Oral corticosteroid is the first-line treatment for DIHS/DRESS. Recurrence is frequently observed during the course of the disease and may require long-term administration of oral corticosteroids (7–9). We report here a case of OFH after prolonged oral corticosteroid therapy for dapsone-induced DIHS/DRESS in a young adult with Henoch-Schönlein purpura.

CASE REPORT

A 26-year-old man presented with a 3-year history of recurrent purpuric lesions on the legs. On examination, palpable purpuric lesions were observed on both legs. Histological findings revealed lymphocytes, neutrophils with nuclear debris and red blood cells around the vessels in the upper dermis, which were compatible with a histological diagnosis of leukocytoclastic vasculitis. Direct immunofluorescence demonstrated IgA deposition on the capillaries in the upper dermis. Anti-nuclear antibody was negative. A diagnosis of Henoch-Schönlein purpura (HSP) was made and dapsone at 75 mg daily was initiated, resulting in resolution of the purpuric lesions. Twenty-six days after the initiation of dapsone, the patient developed a fever, generalized erythematous skin rashes and lymphadenopathy. Laboratory findings showed leukocytosis with eosinophilia and liver dysfunction. Anti-human herpesvirus 6 (HHV-6) IgG antibody titres increased from 10-fold to 320-fold in fluorescent antibody tests. The result of lymphocyte transformation test (LTT) for dapsone was positive. Based on these findings, a diagnosis of DIHS/DRESS due to dapsone was made and oral prednisolone at 40 mg daily was started. This regimen was continued for a total of 21 days, as the erythematous skin rashes on the trunk and liver dysfunction recurred on the 14th day of treatment, followed by 30 mg daily for 3 weeks and 25 mg daily for 2 weeks, culminating in a total of 5 months of corticosteroid use. The erythematous skin rashes appeared during the tapering stage of oral prednisolone. New purpuric lesions were observed on the legs 4 months after the cessation of corticosteroid, which resolved with leg rest alone. Ten months after the withdrawal of corticosteroid, the patient experienced bilateral hip joint pain in the absence of trauma (Fig. 1). An X-ray revealed necrosis of the femoral heads (Fig. 2). In order to receive a surgical operation near his family home, the patient was transferred to another hospital. Magnetic resonance imaging (MRI) of the femoral heads revealed non-traumatic OFH.

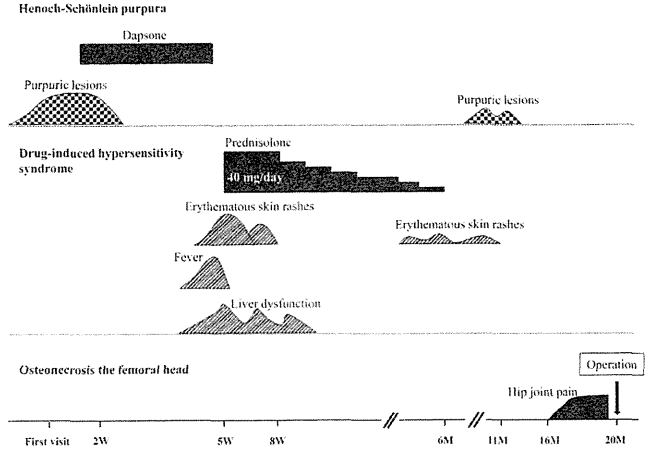

Fig. 1. Clinical course of the patient's conditions. W: weeks after the first visit; M: months after the first visit.

DISCUSSION

Although the pathomechanism of OFH remains unclear, a segment of bone tissue death resulting from the interruption of blood supply to the bone is considered to be responsible for the occurrence of OFH (10). Unlike

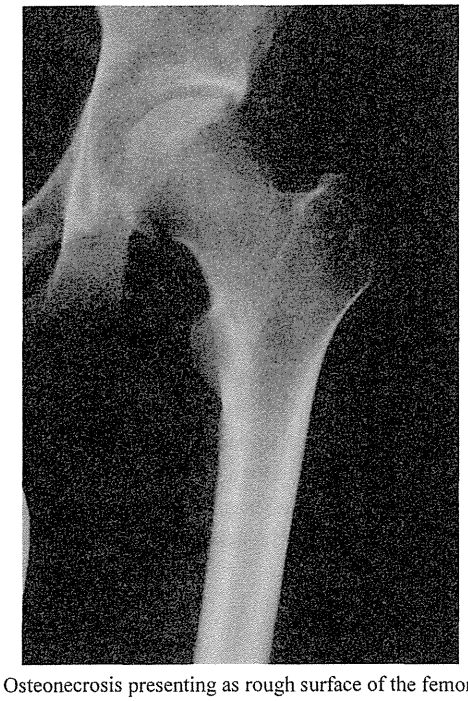

Fig. 2. Osteonecrosis presenting as rough surface of the femoral head.

other adverse effects of corticosteroids, osteonecrosis is irreversible and can be extensive. As the condition most commonly affects male adults in the third and fourth decades of life, the establishment of preventive strategies is required (11). A variety of systemic diseases and conditions are associated with non-traumatic OFH, including collagen diseases such as SLE, antiphospholipid syndrome and systemic vasculitis, in addition to alcoholism, pregnancy, renal transplantation and corticosteroid treatment (1–5).

HSP is a systemic leukocytoclastic vasculitis characterized by cutaneous, articular, gastrointestinal and renal involvement. HSP is generally benign and self-limiting in most cases; however, adult HSP may lead to sequelae, such as myocardial ischaemia and infarction, and bowel ischaemia (12, 13). As OFH has been observed in patients with systemic vasculitis (4), it is likely that the underlying vasculitis in our patient contributed to the development of OFH. The relapse of purpuric lesions on the legs prior to the occurrence of OFH in this patient supports this notion and suggests that regional vasculitis may be a causative factor for bone destruction. The risk of OFH may increase in patients with HSP treated with corticosteroids.

DIHS/DRESS is a severe systemic hypersensitivity reaction caused by specific drugs such as anticonvulsants, allopurinol and dapsone, and involves the reactivation of HHV-6 (6–9). The association between DIHS/DRESS and osteonecrosis has not been reported. In addition, HHV-6 reactivations have not been linked to osteonecrosis.

Oral corticosteroid is the mainstay of treatment for DIHS/DRESS (7–9), and can result in rapid resolution of symptoms within a week after commencement. However, symptom recurrence commonly occurs, thus requiring a longer course of oral corticosteroids, as was noted in our case during the course of the disease.

Studies indicate that corticosteroid therapy is the most common non-traumatic cause of OFH although no data can establish a direct relationship (10). Among OFH patients <40 years, corticosteroid use is the most prominent potential causative agent. The timing of the occurrence of corticosteroid-induced OFH is commonly within several months after corticosteroid administration. Nagasawa et al. (8) have documented that high-dose corticosteroids, >40 mg daily, and pulse therapy could be significant risk factors for OFH in patients with SLE. Inoue et al. (9) have reported that a mean daily dose >25 mg was responsible for the subsequent development of OFH in patients after transplantation. In our patient, the cumulative dose of corticosteroid was 3,446 mg at the end of the 5-month period and the mean daily dose was 21.3 mg.

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The authors declare no conflicts of interest.

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EXPERT REVIEWS

Drug-induced hypersensitivity syndrome: recent advances in drug allergy

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Great strides have been made in the understanding of the pathogenesis and diversity of the clinical symptoms of severe cutaneous adverse drug reactions in the last decade. Among them, drug-induced hypersensitivity syndrome (DiHS) offers a unique opportunity to link between viral infections and the development of severe cutaneous adverse drug reactions, due to its strong association with human herpesvirus 6 infection. This syndrome has several unique features that cannot be solely explained by a drug antigen-driven T-cell activation: they include the delayed onset, paradoxical deterioration of clinical symptoms after withdrawal of the causative drug; unexplained crossreactivity to unrelated multiple drugs; and a variety of long-term sequelae. Dramatic expansions of Tregs observed during the acute stage of DiHS could explain the delayed onset and result in sequential occurrence of viral reactivations. A gradual loss of Treg function occurring after the resolution of DiHS could increase the risk of developing autoimmune diseases as the long-term sequelae. Thus, early recognition of clinical symptoms of DiHS and the frequent monitoring of viral reactivations are essential in improving the short-term or long-term outcomes of DiHS.

KEYWORDS: autoimmune diseases • drug-induced hypersensitivity syndrome • viral reactivations • Treg

According to the WHO definition, an adverse drug reaction (ADR) is 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man' [1]. Much attention has been focused on ADRs, which are immunologically mediated reactions, because they are not predictable and occur independent of the dose administered; they are often referred to as drug allergy or drug hypersensitivity reactions. The skin is one of the most frequently involved organs in ADRs. Most previous studies, therefore, have been performed in relation to cutaneous ADRs. In particular, severe cutaneous ADRs have been investigated more thoroughly.

Severe cutaneous ADRs encompass several distinct clinical entities, the most serious being toxic epidermal necrolysis (TEN)/Stevens–Johnson syndrome (SJS). Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia with systemic symptoms (DRESS) is also a life-threatening multi-organ system reaction. Although the same drugs can often cause these diseases, the two diseases differ in clinical presentation as well as histological findings, prognosis and pathomechanism [2]. Thus, TEN/SJS and DiHS/DRESS represent the opposite ends of a spectrum of severe cutaneous ADRs. While the incidence of TEN/SJS ranges from 0.4 to 6 per million person-years [3], the incidence of DiHS/DRESS continues to increase worldwide probably due to better recognition of this syndrome by doctors or improved population-based surveillance. In addition, more work is presently being carried out to elucidate the epidemiology, diagnosis, complications, long-term sequelae and treatment. Because an excellent review on TEN/SJS is available elsewhere [4–6], emphasis has been placed on DiHS/DRESS in this review.

DiHS/DRESS: a historical overview

The first description of DiHS is generally credited to Meritt and Putnam, who in 1938 reviewed the toxic symptoms caused by phenytoin and noted that the symptoms could be divided into two cutaneous reactions: the first one being a mild, mobilliform eruption that healed upon withdrawal of phenytoin and often did not recur, and

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another type being a severe, exfoliative dermatitis with fever and eosinophilia [7]. Since then it has become clear that the second reaction is also associated with lymphoadenopathy and multivisceral involvement such as hepatitis, and Chaikan *et al.* were the first to describe the systemic implication of this reaction [8]. In 1988, Shear and Spielberg coined the term 'hypersensitivity syndrome' to refer these diverse entities [9]. The term 'hypersensitivity syndrome' could encompass many different entities, including drug allergy and a genetic defect of drug metabolism. Bocquet *et al.* introduced the term 'DRESS' for this syndrome to distinguish it from other severe drug reactions that are not associated with eosinophilia [10]. This syndrome was recognized as a distinct disorder in the early 1960s. Although the term DRESS is still widely used to describe the clinical symptoms, particularly in Europe, in 1998 the alternative term 'drug-induced hypersensitivity syndrome' was proposed based on a case study of patients who developed more severe forms of this syndrome associated with reactivation of human herpesvirus 6 (HHV-6) [11,12]. A retrospective nationwide survey of patients in Japan revealed that reactivations of HHV-6 were detected in the vast majority of patients who satisfy not only the tentative criteria for DiHS but also those reported by Bocquet *et al.* [13]; being a Japanese consensus group, a set of criteria for the diagnosis of DiHS was established in 2006, including HHV-6 reactivation (Box 1 & Figure 1) [14,15]. Although the clinical and laboratory features of this syndrome in its florid form are currently well recognized in Japan, there has been much debate about the inconsistent and variable terminology. While HHV-6 reactivation can be widely used as a specific and sensitive diagnostic clue in Japan, the validity has not necessarily been confirmed in other parts of the world, largely due to an extraordinarily low prevalence of this test. Thus, it remains unknown whether DiHS and DRESS could be part of a continuum of the same disease; that is, DRESS could represent a condition including a clinically mild form of DiHS.

Epidemiology

DiHS has a worldwide distribution but it is undoubtedly underdiagnosed in many countries due to a lack of awareness. DiHS is much more common than SJS and TEN; its true incidence, however, remains unknown because its variable presentation and diverse clinical features and laboratory abnormalities may have resulted in inaccurate diagnosis and reporting. Nevertheless, after clinical manifestations and laboratory findings of this syndrome in its florid form have become widely recognized in Japan, the reported incidence has risen sharply between 2006 and 2008: the incidence could be estimated at more than 10 cases per million in 1 year. Many reports generally agree that DiHS has no age or sex predilection while, in SJS/TEN, women are about 1.5 times more likely to be affected than men. In Japan, the incidence increases steadily with advancing age. Median age at diagnosis is approximately 51.4 years for men and 55.7 years for women (range: 0–83) and only 7% of patients are younger than 20 years. It remains unknown as to whether a racial predilection could exist. There were no seasonal variations. Our series with this syndrome showed no increased incidence of a personal or family history of atopy and drug eruption. Most cases are sporadic. Approximately half of the patients had an infection within the previous 1 month, most commonly viral infections, although the responsible pathogen is not identified.

Diagnosis

The diagnosis of this syndrome is not difficult for Japanese dermatologists who are familiar with the diagnostic criteria established in 2007 (Box 1) [14,15]. However, the diagnosis may be challenging for the doctors who are not familiar with the criteria and may not have experienced cases. Established diagnostic criteria for DiHS, by the Japanese Research Committee on Severe Cutaneous Adverse Reaction, do not differ much from those for DRESS established by an international consensus group named RegiSCAR [16] (a project dedicated to severe cutaneous adverse reactions. The main task of the project is to establish a scientific network of people interested in severe cutaneous adverse drug reactions and to maintain a multinational registry of such cases), except that HHV-6 reactivation is included in the former criteria, but not in the latter.

Box 1. Diagnostic criteria for drug-induced hypersensitivity syndrome established by a Japanese consensus group.

- Maculopapular rash developing >3 weeks after starting with a limited number of drugs
- Prolonged clinical symptoms after discontinuation of the causative drug
- Fever (>38°C)
- Liver abnormalities (ALT >100 U/L)†
- Leukocyte abnormalities (at least one present)
  - Leukocytosis (>11 × 10^9/l)
  - Atypical lymphocytosis (>5%)
  - Eosinophilia (>1.5 × 10^9/l)
- Lymphadenopathy
- 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.
ALT: Alanine aminotransferase; HHV-6: Human herpesvirus 6.
Data taken from [14].

Diagnosis of definite or typical DiHS requires the presence of seven criteria [15]. Probable or atypical DiHS can be diagnosed in patients with typical presentation (criteria 1~5) but in whom HHV-6 reactivation cannot be found due to inappropriate timing of sampling and other reasons. Of note is that the series of >100 patients diagnosed by clinical findings has consistently shown that HHV-6 reactivation can be detected in the vast majority of patients who satisfy the other six criteria (criteria 1~6) (Figure 1) and show clinical manifestations consistent with those reported by Bocquet *et al.* [10], but not in those with other types of drug eruption such as SJS/TEN. By contrast, HHV-6 reactivation is rarely detected in patients with a

tendency toward milder forms of this syndrome. Consistent with this, Tohyama *et al.* reported similar findings [13].

Other inflammatory conditions that are in the clinical differential diagnosis include measles, infectious mononucleosis, Kawasaki syndrome, hypereosinophilic syndrome, drug-induced pseudolymphoma and staphylococcal toxic shock syndrome [17]. Clinical features of DiHS/DRESS can often be misdiagnosed as bacterial infection, which may place a substantial burden on physicians, who are not familiar with this syndrome, to consider unnecessary antibiotic therapy in patients with unexplained illness, such as rash and fever. However, after wide acceptance of the criteria, there has been little disagreement among Japanese dermatologists about the diagnosis of this syndrome with obvious findings. Nevertheless, we should be cautious not to consider that the clinical criteria are all present on any given day, particularly at onset; instead we should consider that the severity of these clinical symptoms at onset provides only a guide to prognosis and is not absolute, as patients usually initially develop two or three features of this syndrome followed by other symptoms one after another. Because eosinophilia is seen at most in 60–70% of patients who satisfy the criteria, the new descriptive term DiHS is recommended in order to avoid confusion due to the lack of consensus in the literature about its terminology. However, the term DRESS is still used frequently in the literature because the criteria for DRESS do not require the measurement of HHV-6 reactivation (Box 2). HHV-6 reactivation, as evidenced by the significant rise in HHV-6 IgG titers or HHV-6 DNA loads, should be used to confirm a clinical diagnosis rather than simply as a screening tool, because this reactivation can be detected at a certain timing, 2–3 weeks after onset or withdrawal of the causative drug (Figure 1), despite such a wide variety of clinical symptoms.

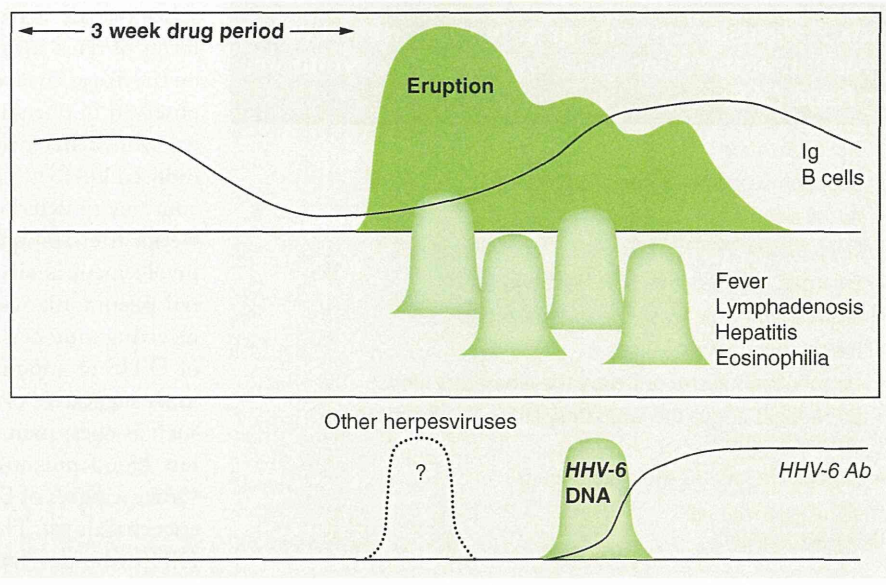

Figure 1. The clinical course of drug-induced hypersensitivity syndrome. This syndrome usually begins with a fever shortly followed by a maculopapular rash >3 weeks after starting therapy with a limited number of drugs, such as anticonvulsants. Patients usually develop two or three features of symptoms followed by a step-wise development of other symptoms. These symptoms continue to deteriorate or several flare-ups can be seen for even weeks or months after stopping the offending drug. Serum Ig levels continue to decrease for a week after withdrawal of the drug. Despite such a wide variety of clinical symptoms, HHV-6 reactivation occurs 2–3 weeks after onset.
Ab: Antibody; HHV-6: Human herpesvirus 6; Ig: Immunoglobulin.
Data taken from [13].

Clinical features

This syndrome typically occurs with fever or cutaneous lesions 3 weeks to 3 months after starting therapy with a limited number of drugs, mainly anticonvulsants (Box 3) [2]. It remains unknown, however, why a limited number of drugs can cause this syndrome because they do not have common epitopes and common pharmacologic actions. Depending on race, significant differences exist among these drugs with regard to the potential to cause DiHS; for example, in Japan, minocycline rarely causes DiHS while mexiletine frequently does, and this is precisely the opposite of that which has been shown to happen in caucasians. Crossreactivity among these drugs has been frequently reported, because phenytoin, phenobarbital and carbamazepine can be metabolized to a hydroxylated aromatic compound and arene oxides are suggested intermediates in the reaction [9]. The delayed onset in relation to the introduction of the causative drug is one of the important features of this syndrome that can be distinguished from other types of drug eruptions, which usually start 1–2 weeks after starting therapy. Indeed, the authors have never seen patients who developed DiHS within 2 weeks after starting therapy. By contrast, DiHS has been reported to develop in patients receiving anticonvulsants for up to 40 years. Upper airway infections are frequently observed as a prodromal symptom in this disease.

The maculopapular or erythematous eruptions are initially observed or the face, upper trunk (Figure 2A) and upper extremities. They may be slightly pruritic and can become confluent. One of the characteristic features of the eruption at the early stage is facial, periorbital or neck erythema and edema studded with pinhead-sized pustules, reminiscent of acute generalized exanthematous pustulosis. Although some erythematous macules may coalesce to form blisters, most erythematous macules do not evolve into blisters and no mucous membrane involvement is usually seen, findings that can be used to differentiate this syndrome from SJS/TEN. Follicular accentuation of the erythematous papules is often observed in the early stage of the rash. The eruption often generalizes into exfoliative dermatitis or erythroderma (Figure 2B), which usually occurs with continued use of the causative drug after onset of the rash. Fever usually precedes the rash by several to a few days and temperature ranges from 38 to 40°C with spikes that may generate concern regarding an

Box 2. Inclusion criteria for potential cases of drug reaction with eosinophilia with systemic symptoms in RegiSCAR.

- Hospitalization
- Reaction suspected to be drug related
- Acute skin rash†
- Fever above 38°C†
- Enlarged lymph nodes in at least two sites†
- Involvement of at least one internal organ†
- Blood count abnormalities
- Lymphocytes above or below the laboratory limits†
- Eosinophils above the laboratory limits (in percentage or absolute count)†
- Platelets below the laboratory limits†

†Three or more required.
Data taken from [16].

underlying infection. Tender lymphadenopathy can be seen in most patients (>70%), particularly early in the illness, predominantly affecting cervical nodes. Bilateral swelling of the salivary glands with severe to mild xerostomia has been seen early in the illness. Importantly, more severe reactions often occur 3–4 days after withdrawal of the causative drug (Figure 2). This paradoxical worsening of clinical symptoms after withdrawal of the causative drug is also characteristic of DiHS and may be mistaken for severe infectious diseases by physicians of first contact to such a case, causing high levels of suspicion of infection: upon the suspicion, unnecessary empirical antibiotic therapy may be started, often resulting in the development of additional drug hypersensitivity. This is because patients with DiHS often show unexplained cross-reactivity to multiple drugs with different structures, including those used after onset of symptoms. Such clinical variability in the presentation allows for a delay in diagnosis, which can lead to significant morbidity.

Liver abnormalities usually occur in the early phase in up to 70% of patients and are characterized by a marked increase in serum alanine aminotransferase. Hepatomegaly accompanied by splenomegaly is frequently observed. In other patients, various forms of renal involvement have also been reported. Depending on the drug, involvement of other organs varies: hepatitis is often observed in phenytoin-, minocycline- or dapson-induced DiHS [17], while renal involvement is particularly evident in allopurinol-induced DiHS [17]. In many severe cases, these variable symptoms continue to deteriorate or several flare-ups can be seen even for weeks after stopping the causative drug. Although pulmonary involvement is rarely reported in patients with DiHS, interstitial pneumonia with eosinophilia is often observed in patients receiving minocycline [17]. Myocarditis can also develop at onset of DiHS or approximately 40 days after onset. Clinical symptoms suggestive of myocarditis include heart failure symptoms such as chest pain, unexplained tachycardia, breathlessness and low blood pressure during the early phase of disease course. Other features of DiHS include coronary artery thrombosis and encephalitis [18]. The authors have recently reported a patient with DiHS who developed limbic encephalitis and the syndrome of inappropriate secretion of antidiuretic hormone long after resolution of rashes [18]. HHV-6 has been suggested to be involved in the limbic encephalitis associated with hyponatremia, although HHV-6 DNA was not detected in the cerebrospinal fluid. Patients with DiHS who developed viral meningitis and herpes zoster 1–2 months after resolution of rashes were also seen. Thus, depending on the sites and severity of organ damage, various clinical symptoms would develop at various time points after onset. Nevertheless, their development may be clinically silent and recognized only months or years later in some patients.

Box 3. Drugs frequently causing drug-induced hypersensitivity syndrome/drug reaction with eosinophilia with systemic symptoms.

- Carbamazepine
- Phenytoin
- Phenobarbital
- Zonisamide
- Mexiletine
- Abacavir
- Lamotrigine
- Nevirapine
- Dapsone
- Salazosulfapyridine
- Allopurinol
- Minocycline

Laboratory findings

This syndrome is characterized by leukocytosis with atypical lymphocytes and eosinophilia of various degrees. Leukopenia or lymphopenia has also been reported and this occasionally precedes leukocytosis [19]. The lymphocytosis is primarily due to an increase in either CD4 or CD8 T-cell counts. Eosinophilia may often be delayed for 1–2 weeks and occurs even after elevations in liver enzymes return to baseline. Elevations in liver enzymes usually persist for several days or weeks after withdrawal of the causative drug but in the vast majority of patients the hepatitis resolves spontaneously, although hepatic necrosis may cause death in the setting of coagulopathy and sepsis [17]. The mortality from DiHS can be approximately 10% in the case series and has been correlated with the degree of renal involvement rather than hepatic involvement [14].

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 (Figure 1) [20]. Approximately 1–2 weeks after the nadir in the decrease, the overshoot in Ig levels is transiently observed and their levels eventually return to normal upon full recovery. Nevertheless, the follow-up analyses of serum Ig levels long after resolution showed that their serum Ig levels tend to be lower than those in healthy controls.

Although HHV-6 was previously thought to be the only herpes virus reactivated during the course of DiHS [11], the recent studies of real-time measurement for viral loads have demonstrated that

other herpes viruses, such as Epstein–Barr virus (EBV), HHV-7 and cytomegalovirus (CMV), are also reactivated during the course of the disease in a sequential order as demonstrated in graft-versus-host disease (GVHD) [21]. Nevertheless, because HHV-6 reactivation can be detected in the vast majority (>70%) of patients with DiHS at a certain time point, 2–3 weeks after onset, but not in those with other drug eruptions, this becomes a gold standard test for identifying patients with DiHS in Japan [14]. According to the sequential analyses of viral loads in patients with DiHS, the cascade of reactivation events initiated by HHV-6 or EBV extends, with some delay, to HHV-7 as well, and eventually to CMV [21]. In view of the similarity between DiHS and GVHD with regard to the clinical manifestations and the order of viral reactivations, frequent deterioration or several flare-ups of clinical symptoms occurring after withdrawal of the causative drug in DiHS could be explained by sequential reactivations of herpes viruses in other organs, which would also occur in a sequential order but totally independent of that occurring in the blood.

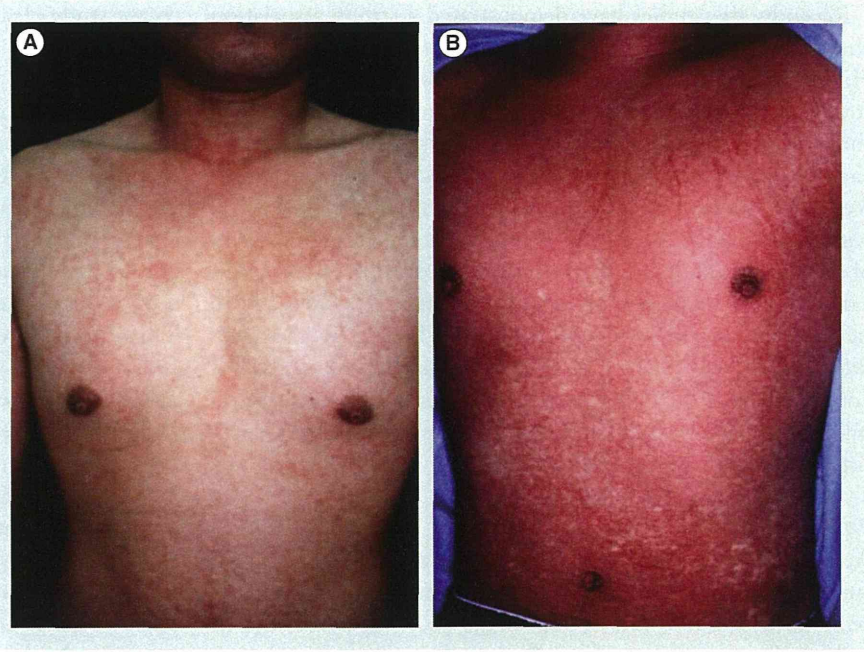

Figure 2. The patient's chest and abdomen on his initial presentation and 4 days after withdrawal of the drug. (A) On his initial presentation, slight erythema can be seen. **(B)** A dramatic deterioration of his symptoms is observed despite withdrawal of the drug.

Pathological findings

The histologic picture of DiHS is superficial perivascular lymphocytic infiltrates composed mainly of T cells with some extravasated erythrocytes or eosinophils [11]. Depending on biopsied lesions, variable degrees of focal spongiosis associated with a lichenoid infiltrate can be seen, but severe epidermal damage as frequently seen in SJS/TEN is never detectable. In some patients with DiHS, a noncaseating epithelioid granulomatous infiltrate or a pseudolymphoma-like infiltrate can be detected in the upper or mid-dermis.

In vitro testing

The lymphocyte transformation test (LTT) is a reliable method to define the causative drug in drug eruptions, when performed at the right timing [22]. In patients with DiHS, false-negative LTT reactions were constantly observed when examined at the acute stage, usually within 2–3 weeks after onset, regardless of whether the patients are on therapy with systemic corticosteroids. Positive LTT reactions were observed when tests were performed after resolution, usually 5–8 weeks after onset [22]. By contrast, totally opposite results were observed in patients with SJS/TEN. Positive LTT reactions were observed when tests were performed in the acute stage but not after resolution.

Genetics

There have been attempts to link susceptibility to DiHS to allelic variations. However, although a strong association has been demonstrated between HLA-*B*1502* allele and carbamazepine-induced SJS/TEN in Han Chinese patients [23], only small cohorts of patients have been analyzed in association studies in which the frequencies of the alleles of interest have been compared between DiHS and control individuals [24,25]. Although the insufficient sample sizes in this study preclude any general conclusions, the results showed that the HLA-*B*1502* allele was not observed in any patients with DiHS or SJS/TEN caused by anticonvulsants and that the HLA-*B*4801* allele was found in six out of the 16 patients with DiHS (37.5%). The frequencies of the HLA-*B*4801* allele in patients with DiHS was considerably higher than the reported frequencies in the Japanese population (4.3%), although the difference is not statistically significant after correction for multiple comparisons [25]. Four out of the six patients with HLA-*B*4801* allele showed severe liver dysfunction (alanine aminotransferase >300 IU/l) during the course of DiHS. Recent studies have also demonstrated a strong association of the HLA-*B*5801* allele and allopurinol-induced DiHS/DRESS [26,27]. The association has also been confirmed in the study (Unpublished Data). In addition, four out of the 16 patients with DiHS had the HLA-*B*1301* allele (25%); the frequency of the HLA-*B*1301* allele in those patients was much higher than that reported for Japanese population (1.3%), although not statistically significant. Interestingly, in three out of the four patients with HLA-*B*1301*, not only HHV-6 but also CMV was reactivated in association with severe liver dysfunction during the course of DiHS. In view of this possible association between the HLA-*B*1301* allele and particular virus reactivation in the study, the effect of certain HLA-*B* alleles on the occurrence of virus reactivations may contribute, at least in part, to the HLA-*B* allele association with the disease.

Recently, the studies have demonstrated a strong association with carbamazepine-induced drug eruptions including DiHS and HLA-*A*3101* in Japanese patients [28]. This was originally demonstrated in patients with carbamazepine-induced DiHS and then this association was also confirmed in patients with other types of carbamazepine-induced drug eruptions. Because the same results were also reported with caucasian patients [29], the association with HLA-*A*3101* is likely to be important for the development of carbamazepine-induced drug eruptions regardless of the clinical phenotype. The clinical phenotype ranging from TEN to maculopapular rash would be determined by additional factors different from the HLA-*A*3101* allele, including viral infections, and the HLA-*A*3101* allele could determine a patient's susceptibility to carbamazepine. Large-scale studies will be necessary for full investigation of candidate alleles.

Pathogenesis

Activated T cells seem to play an important role in DiHS, as suggested in other severe drug eruptions. It was previously believed that DiHS merely represents an exaggerated, hyperinflammatory response with inflammation-induced viral reactivations and subsequent organ injury. In this regard, Picard *et al.* have recently demonstrated that cutaneous and visceral symptoms of DiHS/DRESS are mediated by activated $CD8^+$ effector T (Teff) cells, which are largely directed against herpes viruses, such as EBV [30]. It has now become clear, however, that immune homeostasis in the skin relies on a delicate balance of Teff cells and Treg cells and is disturbed in DiHS (Figure 3). Our recent study clearly demonstrated that dramatic expansions of functional Treg cells were found in the acute stage of DiHS, while their capacity to suppress the activation of Teff cells was profoundly impaired in the acute stage of SJS/TEN [31]. This expansion of Treg cells would occur in an unrecognized fashion to counteract Teff-induced inflammation far before onset of DiHS, which would contribute to not only the delayed onset, but also to viral reactivations. Eventually, however, the delicate balance would be disturbed in favor of Teff cells despite protracted expansions of Treg cells, resulting in an inflammatory outcome. Thus, immune responses during the acute stage of DiHS are characterized by a complex interplay among Teff cells, Treg cells and herpes viruses: the Teff population consists of antiviral Teff and antidrug Teff cells that are dominated by a Th2 phenotype due to their relative resistance to the action of Treg cells. The expanded Treg cells would also limit the severity of Teff-mediated immunopathology. This scenario (Figure 3) provides an explanation for why severe epidermal damage cannot be detected in the skin lesions of DiHS, unlike SJS/TEN lesions, why the onset of DiHS is delayed in relation to the introduction of the causative drug, and why proliferation of drug-specific Teff cells as evidenced by a positive LTT reaction can only be detected at the resolution stage of DiHS, but not at the acute stage. However, a gradual loss of Treg-cell function occurs after the resolution of DiHS, which may result from their eventual exhaustion by persistent or repeated viral reactivations. Indeed, reflecting a loss of Treg cell function after resolution, several autoimmune diseases have been reported to occur at intervals of several months and years after clinical resolution of DiHS: they include Type 1 diabetes mellitus, thyroiditis, SLE and sclerodermoid GVHD-like disease [32,33].

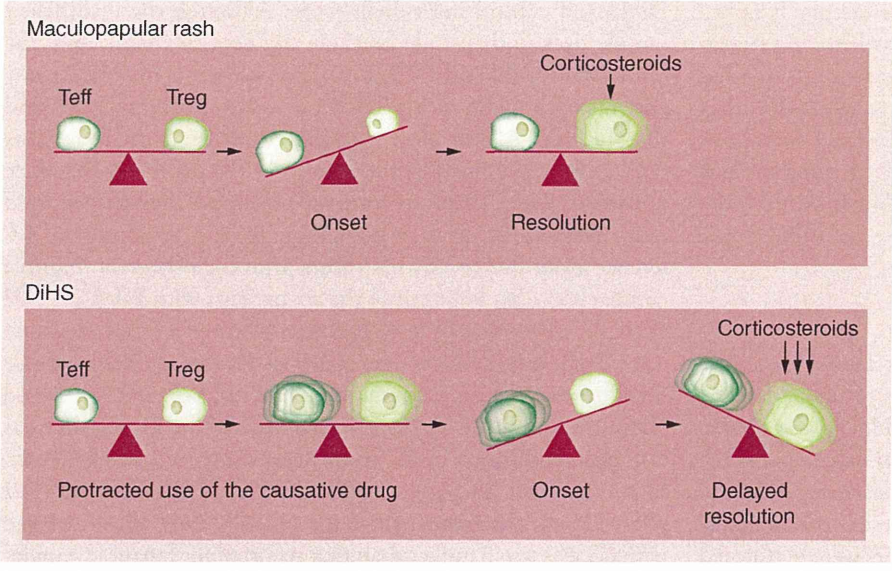

Figure 3. A hypothetical model for the development of DiHS.
In quiescent conditions, the action of effector T cells is under control of Treg cells. Protracted use of anticonvulsants with potentially immunosuppressive activities results in expansions of Tregs that serve to inhibit activation of Teff cells. Eventually, however, a delicate balance between Teff and Treg cells is disturbed, leading to onset of DiHS. Systemic corticosteroids can improve clinical symptoms, probably by their potentiating Treg-cell function.
DiHS: Drug-induced hypersensitivity syndrome; Teff: T effector.

Treatments

Early recognition of this syndrome is the most important step in treatment and is essential in improving patient outcomes, because many physicians are not familiar with this syndrome. Empirical treatment with antibiotics or nonsteroidal anti-inflammatory drugs should not be done even in DiHS patients with a high-grade fever during the acute stage, which may confuse or worsen the clinical picture probably due to unexplained crossreactivity to multiple drugs, a finding frequently seen in patients with DiHS [34].

Despite the lack of large controlled trials, corticosteroids are the immunosuppressive agent most frequently used for the treatment of DiHS and the most consistently effective. The usual dosage is prednisolone 40–60 mg/day. They are administered for 2–3 months. Systemic corticosteroids need to be tapered over

6–8 weeks to prevent the relapse of various symptoms of this syndrome. In this regard, the authors have recently reported two patients with DiHS who subsequently developed cutaneous and gastrointestinal CMV ulcers. In one patient, fatal CMV enterocolitis developed soon after tapering the dose of oral prednisolone [35]. Because the retrospective studies showed that older and male patients with antecedent high HHV-6 DNA loads are at risk of subsequently developing CMV disease that may be fatal, patients with DiHS treated with corticosteroids should be monitored carefully for the development of CMV disease.

Thus, once systemic corticosteroids have started, drug dose should be reduced gradually even upon resolution of clinical manifestations in DiHS, because patients with DiHS are at greater risk of subsequently developing the wide spectrum of immune reconstitution syndrome (IRS) ranging from CMV diseases to autoimmune diseases [36,37] and the use of systemic corticosteroids represents an important factor that increases the risk of disease progression to full manifestations of IRS upon withdrawal or reductions. Given the high risk of sequelae from CMV reactivation in patients with DiHS, the direct anti-CMV medications with stepwise withdrawal of corticosteroids may help to avoid disease progression to full manifestations of IRS.

Conclusion

Although great strides have been made in the understanding of the pathogenesis of DiHS, several important questions remain unanswered. They include the following: What is the precise role of viral reactivation in organ injury? Is there an efficient treatment that can be used to reduce the risk of subsequently developing autoimmune diseases? Why are Treg cells specifically expanded at the acute stage of DiHS? How do Treg cells lose their functional activity upon clinical resolution of DiHS? Thus, the relevant future research agenda is multifaceted. First, it should be emphasized that the prevalence of DiHS in Japan has 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 increasing the availability of the diagnostic test, so that all patients who need treatment can be identified. Second, the development of novel assays that can simultaneously detect reactivations of various herpes viruses and their subsequently validation will be of great use. Third, 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.

Expert commentary

Prompt recognition of DiHS as a distinct phenotype of severe cutaneous ADR associated with viral reactivations could help physicians to determine the appropriate next step when a complex sequence of events as described above occurs, thus improving the morbidity and mortality of this otherwise life-threatening disease. Although this syndrome was recognized as a distinct disorder in the early 60s, much confusion resulted from the inconsistent and variable terminology used and the lack of a specific and sensitive diagnostic test. Although there is no fundamental difference in the clinical and laboratory findings, except for HHV-6 reactivation, between DiHS diagnosed by our criteria and DRESS diagnosed based on the standardized scoring system proposed by the RegiSCAR group [2,16], HHV-6 testing can be used to confirm a clinical diagnosis rather than simply as a screening tool. Nevertheless, this testing is not necessarily available in many countries other than Japan. The development of an internationally standardized scoring system, therefore, is needed to clearly identify patients with DiHS without the aid of HHV-6 testing. Although systemic corticosteroids have become accepted as the gold standard treatment for ameliorating clinical symptoms of DiHS, it remains to be determined whether this treatment is also beneficial from a viewpoint of various important outcomes including time to discharge, death and disability after 1 year. In this regard, the unpublished longitudinal studies have showed that treatment with systemic corticosteroids was beneficial for the long-term outcomes such as the subsequent development of autoimmune diseases and autoimmune phenomena. Clinicians should recognize, however, that these anti-inflammatory therapies aiming at relieving the symptoms in the acute stage of DiHS need to be balanced with antiviral therapies aiming at reducing the amplitude and duration of tissue burden of viruses reactivated.

Five-year view

The measurement of herpesvirus reactivations would represent a valuable diagnostic tool, when used in combination with other well established tests such as LTT, in identifying patients with DiHS/DRESS in many countries other than Japan. The development of treatments for patients with DiHS/DRESS critically depends on our understanding the mechanism by which herpesviruses can be reactivated in a sequential manner after onset of this disease. Treg cells are likely to be central to the mechanism and would represent potential targets for future therapeutic approaches that can ameliorate inflammatory responses at the acute stage while preventing the subsequent development of harmful outcomes, such as autoimmune diseases.

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Key issues

- Drug-induced hypersensitivity syndrome (DiHS) is a life-threatening, multi-organ systemic reaction characterized by fever, rash, hepatitis, lymphodenopathy and leukocyte abnormalities such as eosinophilia.
- This syndrome has been reported under different names, including drug reaction with eosinophilia with systemic symptoms (DRESS).
- The causative drugs are very limited and the most frequent drugs are anticonvulsants.
- The series of >100 patients diagnosed solely by clinical findings have consistently shown that human herpesvirus 6 reactivation can be detected at a certain timing, 2–3 weeks after onset in the vast majority of the patients, despite a wide variety of clinical symptoms.
- Established diagnostic criteria for DiHS established differ from those for DRESS in that reactivation of human herpesvirus 6 is included in the former criteria.
- Positive lymphocyte transformation test reactions were observed when tests were performed after resolution, usually 5–8 weeks after onset, but not at the acute stage.
- Dramatic expansions of Tregs observed during the acute stage could explain various clinical and laboratory findings and result in the sequential reactivation of herpes viruses.
- Several autoimmune diseases have been reported to occur at intervals of several months and years after clinical resolution of DiHS.

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to the Wickham striae) surrounded by dotted or linear vessels *(figure 1D)*. In contrast, the atrophic plaque on the sacrum showed structureless white areas and chrysalis structures [5] and diffusely arranged elongated, partially looped telangiectasias of different lengths and calibers *(figure 1E)*. Finally, dermoscopy of the hyperpigmented plaque allowed the observation of fine lilac vessels arranged in a ring-like distribution *(figure 1F)*. Due to the dermoscopic polymorphims, biopsies were taken from one papule on the leg, the sacral plaque and from the peripheral border of the hyperpigmented plaque on the abdomen; subsequent histopathologic examination revealed LP, extragenital LS and morphea, respectively.

The diagnosis of LP was based on the presence of compact orthokeratosis, wedge-shaped hypergranulosis, irregular acanthosis, a dense band-like infiltrate, predominantly of lymphocytes, in the papillary dermis, accumulation of melanophages and vacuolar alteration of the basal layer.

Histopathologically, LS revealed a compact hyper- and orthokeratotic scale with follicular plugging and an atrophic epidermis with vacuolar alteration of the basal layer; a zone of pallor (lymphedema) in the papillary dermis and an interstitial lymphocytic inflammatory infiltrate in the medial dermis were present.

The diagnosis of morphea was based on the presence of dermal sclerosis with swollen collagen fibers and decreased spaces between collagen bundles of the reticular dermis; in addition, a moderately perivascular inflammatory infiltrate of lymphocytes and loss of adnexal structures were noted.

Standard laboratory tests, antibodies against thyroid and antinuclear antibodies, antinuclear antibodies (ANA), IgG and IgM Borrelia serology, as well as hepatitis A, B and C virus serology were within normal ranges or negative.

To our knowledge, our patient represents the third documented case of co-existing LP, LS and morphea. Despite the rare co-occurrence of all three entities, our case suggests that dermoscopy not only aids clinical recognition, by revealing different patterns in each corresponding entity, but may also guide selection of the most representative lesion for biopsy. ■

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Diffuse large B-cell lymphoma as a sequela of Stevens-Johnson syndrome associated with an increased Epstein-Barr virus load

Little attention has been paid to long-term sequelae developing years after complete recovery of Stevens-Johnson syndrome (SJS) [1]. We present a SJS patient who developed diffuse large B-cell lymphoma (DLBCL) two years after complete resolution of SJS.

A 48-year-old woman was treated with minocycline, and then cefcapene pivoxil (CFPN PI) for pneumonia. On days 7 and 14 of the treatment with CFPN PI and minocycline, respectively, an eruption appeared on the trunk and face. Examination revealed high-grade fever (38.5°C), widespread erythematous macules with erosions *(figures 1A, B)*, and severe erosive lesions on the lips; conjunctivas were hyperemic. No cervical lymphadenopathy was detected. Histology of a biopsy from the flat

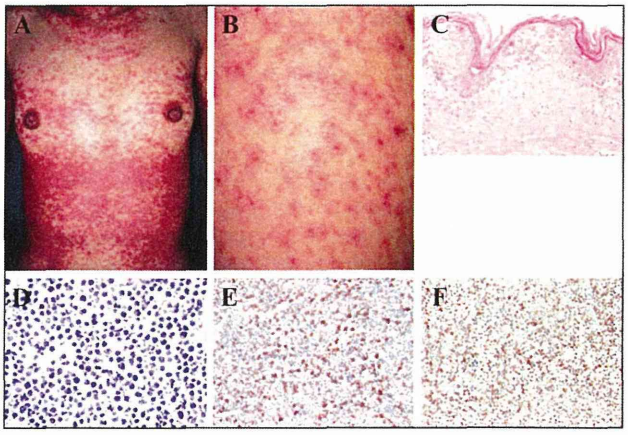

Figure 1. A) Erythematous macules with erosions on the trunk.
B) Atypical target lesions on the thigh.
C) Epidermal necrosis with a mild lymphocytic infiltration in the upper dermis (hematoxylin and eosin stain; original magnification X 100).
D) Atypical lymphoid cells in the cervical lymph node (hematoxylin and eosin stain; original magnification X 400).
E) Positive CD20 expression on atypical lymphoid cells in the lymph node (original magnification X 200).
F) Positive Bcl-2 expression on lymphoid cells in the lymph node (original magnification X 200).

erythematous abdominal macule showed epidermal necrosis and a mild lymphocytic infiltration in the upper dermis *(figure 1C)*. Direct immunofluorescence demonstrated no depositions. Laboratory findings on admission: white blood cell count 3.7×10^9/L with no atypical lymphocytosis or eosinophilia, with mild liver dysfunction. Anti-Epstein-Barr virus (EBV) virus capsid antigen (VCA) IgG titer, anti-EBV VCA IgM titer and EBNA were 640-fold, 10-fold>, and 20-fold, respectively. EBV DNA loads were 440 copies/10^6 leukocytes. Chest X-ray was normal.

After the SJS diagnosis, treatment with systemic corticosteroids 50 mg daily was initiated. Her eruptions steadily improved, corticosteroids were tapered to 60% over 4 weeks and zero over 8 weeks. To determine the causative agents of SJS, lymphocyte transformation test (LTT) was performed on the second day of admission. Positive LTT reactions for CFPN-PI and minocycline were obtained. No significant increases in anti-human herpesvirus 6 (HHV-6) IgG titers or HHV-6 DNA loads were detected during the course of the disease. This patient had persistently detectable levels of EBV DNA (150-280 copies/10^6 leukocytes) for 5 months after complete resolution. 9 months after resolution, the viral load declined.

Two years later, when the EBV load was undetectable, she noticed swelling of cervical lymph nodes and a high-grade fever. Examination revealed a large subcutaneous mass in the neck and multiple palpable axillary and inguinal lymph nodes. Anti-EBV VCA IgG titer, anti-EBV VCA IgM titer and EBNA were 640-fold, 10-fold>, and 40-fold, respectively. Computed tomography scan showed multiple lymph nodules around the aorta and splenomegaly. A cervical lymph node biopsy revealed marked proliferation of atypical lymphoid cells *(figure 1D)* and immunohistochemical stainings for CD 20 *(figure 1E)*, CD 79, CD 10, and Bcl-2 *(figure 1F)* showed strong immunopositivity. Positive EBV-encoded small RNA (EBER) staining cells were not detected. DLBCL was diagnosed. Despite a good response to combination therapy with rituximab and CHOP, she died of pneumonia from opportunistic infections.

As the EBV DNA load was more than 8 times that in asymptomatic EBV carriers in our study, elevated EBV DNA loads may predispose the development of lymphoma. DLBCL is thought to arise from EBV-immortalized B cells which escaped T-cell surveillance, suggesting that the impairment of anti-EBV immunity during SJS results in uncontrolled, EBV-driven B cell proliferation in the absence of adequate T-cell surveillance [2, 3]. EBV-specific immunity in this patient may have exhibited a reduced ability to control the outgrowth of EBV-infected B cells during SJS. The EBV load during the acute stage of SJS was higher than after resolution and persistence was observed even during resolution, this patient may have had defects in long-term anti-EBV immunity. Interestingly, the persistently elevated EBV load declined just prior to the development of DLBCL.

Other factors, particularly those associated with drug therapy, may also be important. Systemic corticosteroid use has been associated with an increased risk of non-Hodgkin lymphoma [4, 5]. However, systemic corticosteroids were only given for 8 weeks in this patient; it is implausible that the DLBCL would be caused by such a short exposure. The causative drug of SJS may also have influenced the risk of lymphoma development because minocycline is well known to have the potential to cause lymphoproliferative disorders [6]. This is also unlikely, however, in view of the duration of exposure.

Our case emphasizes the importance of long-term follow-up in patients with SJS. ■

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Basal cell carcinoma which developed on the surface of recurrent parotid pleomorphic adenoma: coincidence or causality?

Pleomorphic adenoma is the most common benign tumor of salivary gland and basal cell carcinoma (BCC) is the most common cutaneous malignant tumor. Coexisting pleomorphic adenoma and BCC has rarely been reported.

A 66-year-old female complained of a painless enlarging mass on her left post-auricular and mandibular area. She had received tumor excision on the same area ten years ago. The pathology report was a benign pleomorphic adenoma at that time. Several years later, the patient found recurrence of the subcutaneous tumor and a gradually enlarging red plaque above the tumor. The patient denied any systemic

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the virus would have disappeared. In this regard, we have recently demonstrated that the presence of VZV antigens in eccrine epithelium can be persistently detected even long after clinical resolution of HZ, for instance, 2.5 years after the clinical resolution, when VZV DNA was no longer detected [8].

These observations prompted us to identify the presence of the VZV antigens in the lesions of the unilateral, linear or zosteriform variant of LP. The aim of the present study was to determine whether VZV antigens could be detected in either the zosteriform or linear LP lesions, or whether the presence of VZV antigens could be used to differentiate the zosteriform LP from the linear LP. Here we describe 2 cases of zosteriform LP without apparent prior episodes of HZ, in whom VZV antigens can be detected in the sweat glands and ducts. Interestingly, these patients showed hypohidrosis localized to the LP lesions (data not shown). VZV should be included in the list of infectious agents that can trigger LP, particularly in the unilateral, zosteriform variant. Our study provides evidence indicating that immunohistochemical detection of VZV antigens in sweat glands and ducts should be included in the diagnostic scheme of LP arising in the resolved HZ lesions and that zosteriform LP may represent a clinical entity distinct from linear LP while linear LP is reserved for conditions following the lines of Blaschko. Thus, the definition of zosteriform LP and linear LP could also be based on a judgment about pathogenesis.

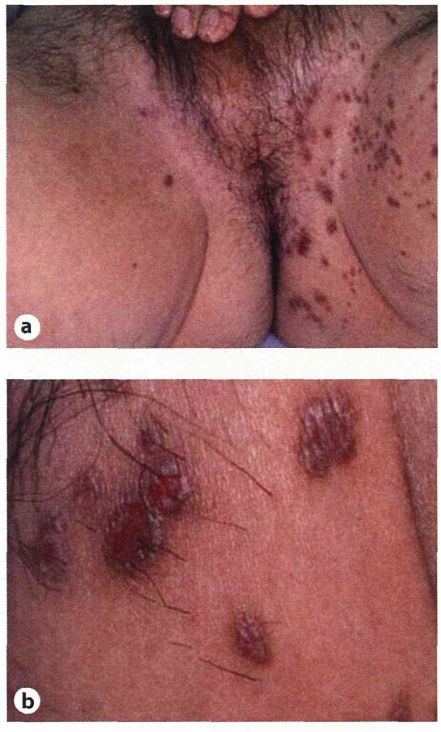

Fig. 1. a Case 1. The distribution of lesions is consistent with his left L2 dermatome. **b** Multiple violaceous, flat-topped, polygonal papules are noted in the inner aspect of the thigh.

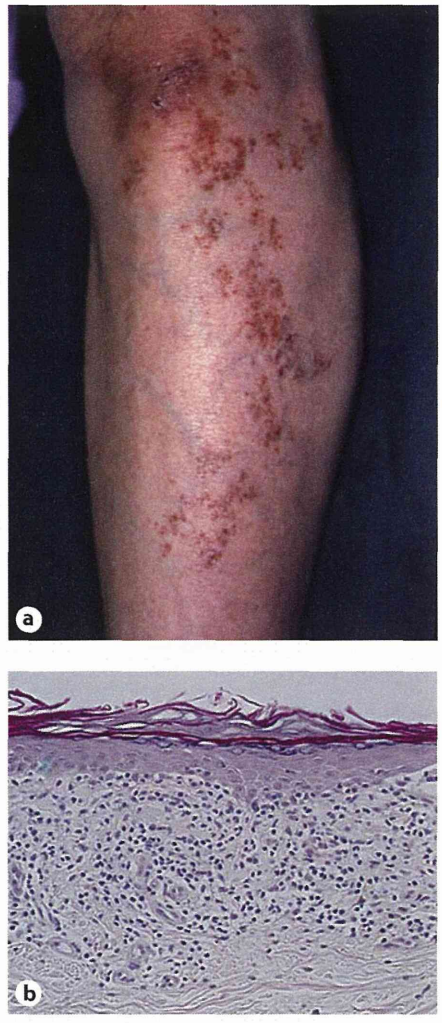

Fig. 2. a Case 2. Multiple violaceous, erythematous papules affect the extensor aspect of the left lower leg in the L5 dermatome. **b** Liquefaction degeneration and a band-like inflammatory infiltrate in the papillary dermis in his lesion. Hematoxylin-eosin staining. Original magnification ×60.

Patients and Methods

Case 1

A 39-year-old man was referred with unilaterally distributed, pruritic eruptions, several of them located on the left upper thigh. Five years prior to his initial presentation, the patient had noted asymptomatic erythematous eruptions on the thigh, although more detailed information was unavailable. Within 2 weeks after onset of the eruption, the lesion expanded upwards to the left side of the scrotum with a marked midline cutoff and also downward along the flexor surface of the thigh to the left knee. The zosteriform distribution of the grouped papular lesions was consistent with his left L2 dermatome (fig. 1a). The lesions consisted of violaceous, flat-topped, polygonal papules with a central depression (fig. 1b). Fever or systemic symptoms were absent. There was no nail or mucous membrane involvement. No signs of viral infection were found. Histopathological examination obtained from the lesions on the thigh revealed hydropic degeneration of the dermoepidermal interface with sporadic Civatte bodies and a band-like inflammatory infiltrate in the papillary dermis, consistent with the diagnosis of LP. The VZV titer in serum was positive but no further increase or decrease was detected 3 weeks later.

Case 2

A 76-year-old man presented with a 1-month history of asymptomatic linear erythematous to purplish lesions on his left lower leg (fig. 2a). Although no prodromal pain was experienced, the patient recalled that he had bruised the left knee 3 months prior to his initial presentation. Examination revealed erythematous, slightly raised papules, arranged in the left L5 dermatome. A skin biopsy obtained from the erythematous lesion showed typical features of LP, including liquefaction degeneration and a band-like inflammatory infiltrate in the papillary dermis (fig. 2b). Based on clinical and histological findings, a diagnosis of zosteriform LP was made. The VZV titer in serum was positive.

Table 1. Characteristics of patients with zosteriform and linear LP

Patient No./ age/sex	Clinical findings				VZV antigen in eccrine epithelium
	distribution pattern of lesions	involved sites	serum anti-VZV IgG titer	underlying diseases	
Zosteriform					
1/39/M	L2	thigh	10.1		+
2/76/M	L5	leg	23.4		+
3/26/F	S1	leg	30.5		+
4/55/M	L3	buttock, thigh	31.1	hepatitis C	–
5/70/F	S1	buttock, leg	10.9	hepatitis C	–
Linear					
6/71/F	BL	buttock, leg	6.7		–
7/38/F	BL	leg	13.4		–
8/71/F	BL	leg	69.7		–

BL = Blaschko line; anti-VZV IgG titer = measurement at the first visit; zosteriform = lesions showing a dermatomal distribution pattern; linear = lesions following the lines of Blaschko.

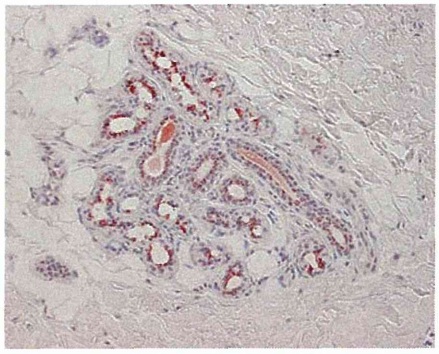

Fig. 3. VZV antigen is expressed in sweat glands and ducts in case 1. Original magnification ×60.

Immunohistochemical Analyses of VZV Antigen in LP Lesions

Our previous studies demonstrated that VZV antigen expression is observed in the cytoplasm of eccrine gland and duct epithelium in the majority of HZ lesions up until 2.5 years after the onset of HZ [8]. These findings prompted us to investigate whether VZV antigens could be detected in zosteriform and linear LP lesions. Biopsy specimens were obtained from these LP lesions of 6 additional patients with informed consent. To detect VZV antigens in these LP lesions, immunohistochemical examinations were performed using paraffin sections of formalin-fixed materials, murine monoclonal antibody directed to the VZV envelope glycoprotein E (gE; Chemicon Inc., Temecula, Calif., USA), and the Dako Envision System (Dako, Calif., USA), as described previously [8]. Briefly, 5-μm sections were deparaffinized and rehydrated. After washing in phosphate-buffered saline, they were rinsed in 3% H_2O_2 for 10 min to block endogenous peroxidase activity. The sections were then incubated with VZV gE antibody overnight at 4°C. These sections were counterstained with hematoxylin.

Results

The clinical data and histological characteristics of the 8 LP biopsy specimens including those from cases 1 and 2 are summarized in table 1. None of these patients were under immunosuppressive therapy. None of these patients had a history of previous HZ and a significant increase in serum VZV IgG titers. These LP lesions were divided into two categories, based on the distribution pattern of the lesions, 'zosteriform' and 'linear': 'zosteriform LP' was defined as LP lesions showing a dermatomal distribution pattern, and 'linear LP' was defined as those following the lines of Blaschko. Cases with intermediate or overlapping forms of LP lesions that were judged neither 'zosteriform' nor 'linear' in the distribution pattern were excluded from this analysis.

As shown in figure 3, VZV gE was detected in the cytoplasm of eccrine gland and duct epithelium associated with no cytopathic changes in 3 of the 5 zosteriform LP lesions, but not in the 3 linear LP lesions. Nevertheless, gE immunoreactivity was never observed in epidermal keratinocytes and follicular epithelium in any LP lesions.

Discussion

LP in a unilateral linear distribution has been reported previously by different names, linear LP or zosteriform LP [4–6, 9–11]. Because the distribution patters of these LP lesions do not consistently separate zosteriform from linear LP, distinctions between both variants are difficult to determine solely based on clinical findings. Although a zosteriform LP has generally been regarded as being synonymous with a linear LP, Happle [1, 12] argued that a clear distinction exists between the linear and the zosteriform variants. Indeed, the dermatomal distribution of LP lesions in our patients (cases 1–5) strikingly differed from an orientation along Blaschko's lines. Furthermore, our immunohistochemical study clearly showed that VZV gE was exclusively detected in the sweat glands and ducts of the zosteriform vari-

ant but not in those of the linear variant, in which the LP lesions exhibited a distribution pattern following Blaschko's lines. These results could now be interpreted such that most, but not all, of the zosteriform variant would develop at the site of healed HZ, regardless of whether the HZ lesions were either symptomatic or asymptomatic. Thus, there was good concordance between the original diagnosis established with the distribution pattern and immunohistochemical findings. There are few reports demonstrating VZV DNA itself in LP lesions, regardless of the clinical manifestations [13]. The negative PCR results in the LP lesions supported the view that there is no association between VZV infection and the development of LP. In this study, however, we provided evidence indicating that many lesions of zosteriform LP, but not linear LP, would occur at the healed site of previous HZ lesions, probably zoster sine herpete lesions. These results suggest that VZV infection could be involved in the pathogenesis of LP in a subgroup of LP in a striking unilateral, zosteriform distribution pattern, although we could not totally exclude the possibility that VZV reactivation may also be relevant for the induction of linear LP.

Several clinical and laboratory observations have been reported to suggest the possibility of different pathogenic factors in LP [14, 15]. Among them, a viral etiology has been suspected in view of the association with viral infections such as hepatitis C virus (HCV) and VZV [4–6, 16]. In the literature of LP associated with VZV infection, LP followed the onset of HZ: they had LP lesions at healed HZ scars or at the site of a prior HZ eruption [4–6]. However, our patients had no apparent episodes of HZ, although the most unusual aspect of our patients was its initial zosteriform distribution; moreover, the distribution of the lesions did not correspond with the lines of Blaschko. Owing to our use of immunohistochemical detection of VZV gE protein, we successfully detected VZV protein in eccrine units of the LP lesions.

There are at least three possible mechanisms either acting independently or together, by which VZV infection can trigger the development of LP in these patients. First, the LP may represent true immunological sequelae of VZV infection: the LP may have developed as an immunological reaction to viral proteins that persist in the lesional eccrine units. In this possibility, an unrecognized VZV reactivation could have been the initiating events. Not in accordance with this possibility is our observation that detection of VZV gE was neither associated with viral cytopathic changes in the eccrine units nor with severe inflammatory infiltrates around and in the eccrine units. These findings give no support to the notion that the LP is a direct result of VZV antigen-directed immune responses.

The second possible explanation of the role of VZV in the development of LP would be that the LP represents a variant of the recall phenomenon or the isotopic response. Despite the absence of an apparent history of HZ, a new unrelated disease, that is LP, may appear at the site of previously unrecognized subclinical HZ. Indeed, LP has been shown to have a propensity to occur at the sites of previous injury or inflammation [17, 18]. The third possible explanation is that VZV reactivation may be triggered by local unrecognized trauma within the LP lesions. According to this explanation, tolerance to an antigenetically aberrant cutaneous cell clone could be abrogated by VZV reactivation. This possibility is unlikely, however, because the LP lesions have remained limited to the initial area without further significant extension in the corresponding dermatome, such as the lower leg, during the disease process.

Another possible explanation that we favor is that the presence of VZV in eccrine units may serve to worsen the sweating function thereby acting as a trigger for the subsequent development of LP. In support of this possibility, we have recently noted that hypohidrosis is a sequela frequently observed in the healed HZ lesions [Inoue K. et al., submitted] as well as the zosteriform LP lesions in this study and suggested that sweat leaked from the ruptured ducts into the dermis due to duct blockage or dysfunction at the superficial acrosyringium which would trigger the development of a lichenoid tissue reaction. This explanation is supported by previous studies describing selective sweat gland damage in patients with lichenoid dermatosis and toxic epidermal necrolysis [19, 20]. In our preliminary study, we found sweating dysfunction limited to LP lesions in which VZV antigens were detected in their eccrine units, and the sweating dysfunction was restored to normal levels upon clinical resolution of LP lesions (data not shown).

Interestingly, VZV antigens were not detected even in the zosteriform LP lesions of 2 HCV-infected patients (cases 4 and 5). In view of the notion that the inciting trigger in many cases of LP is an infectious agent and that among the implicated pathogens are HCV, transfusion-transmitted virus, human herpesvirus 6, herpes simplex virus and VZV [15], our results could now be interpreted as suggesting that the etiological agent of LP may vary in each patient: VZV and HCV would trigger onset of zosteriform LP but in a different and exclusive way. Alternatively, interferon α therapy used for the treatment of HCV infection in our 2 cases may have served to eliminate VZV infections in the sweat glands and ducts.

This report illustrates the usefulness of gE monoclonal antibody on biopsy specimens to demonstrate involvement of VZV infection in the pathogenesis of LP, particularly a zosteriform variant of LP, confirming the importance of this finding as a criterion for the diagnosis of LP arising in the HZ lesions. Our findings suggest that LP occurring in a dermatome previously involved by HZ, including zoster sine herpete, could not be so rare as previously thought, but the link between the HZ and the subsequent development of LP would be unrecognized unless special attention has been paid. In this regard, zosteriform LP offers a unique opportunity to link between HZ and LP. Our study provides evidence for the fact that zosteriform LP can be pathogenetically distinct from linear LP and should not be considered a subtype of linear LP.

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Disclosure Statement

There is no conflict of interest.

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◆特集／薬疹の今

DIHSと免疫再構築症候群

平原和久*　塩原哲夫**

Key words：薬疹(drug eruption)，薬剤性過敏症症候群(drug-induced hypersensitivity syndrome)，免疫再構築症候群(immune reconstitution inflammatory syndrome)，後天性免疫不全症候群(acquired immunodeficiency syndrome)，サイトメガロウイルス(cytomegalo virus)

Abstract　薬剤性過敏症症候群(DIHS)は重症薬疹の一つだが，SJS/TENと異なり治療経過中にさまざまなウイルスの再活性化が起こるため，長期予後が問題となる．実際，急性期を過ぎて経過を見ていくと，重篤な合併症を生ずることがあり，死亡例を経験することも多くなってきている．特に，初期に軽症のように見えても，長い経過中急激に悪化する例もあり，一元的に治療方針を決定することは極めて難しい．そのため，DIHSの治療方針は個々の症例ごとに検討していく必要がある．個々の症例における治療方針を決定する際に，極めて参考になる概念がある．それはHIV感染症に対する治療開始後に見られる病態として知られる免疫再構築症候群(IRIS)という概念である．DIHSの病態はこのIRISに極めて類似しているため，この概念を念頭に入れながら，DIHSの治療を考えることにより予後を向上させることができる．本稿では，DIHSの治療を行っていくうえで，この概念をどのように用いていくかを中心に述べていくことにする．

はじめに

重症薬疹にはStevens-Johnson症候群(SJS)，中毒性表皮壊死症(toxic epidermal necrolysis；TEN)，薬剤性過敏症症候群(drug-induced hypersensitivity syndrome；DIHS)があり，そのうえでTENは最重症の薬疹と考えられている．しかし，SJSやTENでは近年になり，厚生労働科学特別研究事業の重症薬疹研究班により重症薬疹の治療指針が示され，早期から適切な治療が行われるようになってきたこともあり，死亡率は減少してきている．一方，DIHSもTEN同様死亡率は高いと考えられるが，治療指針についてはいまだに確立していない．その理由として，DIHSでは初期に軽症と捉えられても症状が遷延化する例が多く，初期の臨床所見に基づいて重症度を判定することが極めて難しいことが挙げられる．というのもDIHSではSJS/TENと異なり，急性期を過ぎても多種のヘルペスウイルスの再活性化が続くため，急性期の治療が終了した後に自己免疫疾患を発症したり，ときに死亡する症例も少なくないからである．これらの要因が，一元的なDIHSの治療法の確立を難しくしている．そうは言っても，我々は目の前のDIHS患者を治療していかねばならないわけで，その際にはなんらかの指標をもつ必要がある．そのための指標として有用な概念がある．それはAIDSの治療時に引き起こされる病態としての免疫再構築症候群(IRIS)という概念である．DIHSの病態を一種のIRISと考えると，DIHSの病態が理解しやすくなり，それが個々のDIHS症例の治療を考える際に極めて有用となる．

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免疫再構築症候群

1．疾患概念

高活性抗レトロウイルス療法(highly active anti-retroviral therapy：HAART)が1997年から本邦でも導入されるようになり，ヒト免疫不全ウイルス(human immunodeficiency virus：HIV)感染症および後天性免疫不全症候群(acquired immunodeficiency syndrome：AIDS)の予後は著しく改善してきている．しかしHAART療法を施行した数週～数か月後に，沈静化していたはずの日和見感染が再び悪化したり，新たな感染症が引き起こされる症例が増えてくる．これは免疫不全状態で増加した病原体に対する免疫応答が治療により急激に回復し，それに伴って起こる過度の活性化は炎症反応の増悪として認められることになる．この現象は免疫再構築症候群(immune reconstitution inflammatory syndrome：IRIS)[1]という概念で一括される(表1)．この概念を知れば知るほど，これまで免疫不全による日和見感染症と見なされてきた病態のうち多くのものが，このIRISにほかならないことが理解できるようになるはずである．HIVは主に$CD4^+$細胞に感染するため，HIV感染症が進行するにつれて$CD4^+$細胞が減少し，宿主の免疫能は徐々に低下していく．それが病原体に対する免疫応答の低下をもたらす結果，それらの病原体は増加する．しかし，免疫応答が低下しているため，明らかな炎症反応は起きず，病原体を排除することもできない．そこに抗HIV薬が投与されることでHIV RNA量が減少し，$CD4^+$細胞数は増加する．そればかりか，単球やマクロファージ，NK細胞の機能も回復してくる[2]．それらの回復は，それまで眠っていた病原体に対する免疫応答を目覚めさせることになる．その結果，それまで増加していた病原体に対して過度の免疫反応(すなわち炎症反応の増悪)が生ずることになる．この炎症反応は免疫応答の回復が急激であればあるほど，強く起こる．実際，Shelburneら[3]はIRISを起こした症例では，抗HIV治療開始後のHIV RNA量減少が速やかで，顕著であることを報告している．つまりIRISは抗HIV治療の抗ウイルス効果が良好であるときに発症しやすいという，一見矛盾した現象を呈することになる．これこそが，多くの臨床家を惑わす最大のポイントなのである．さらに現在の薬剤ではHIV感染症の根治は不可能であり，抗ウイルス薬の副作用や薬剤耐性ウイルス出現の問題から，最近では治療開始時期を遅らせるようになったことも，この現象を起こしやすくさせていると考えられる．このような現象は，今後HIVに対する強力な治療が出現するほど症状が強くなり，症例数も増加していくことが予想される．

表1．IRISの診断ポイント(文献3を引用改変)

①HIV感染陽性
②HAART療法を施行後に生じた変化
○治療前値と比較してHIV-1 RNA量が減少
○治療前値と比較して$CD4^+$細胞数が増加
③炎症反応に矛盾しない臨床症状
④臨床経過が以下のことで説明できない
○既に診断されている日和見感染の予測される経過
○新たに診断された日和見感染の予測される経過
○薬剤の副反応

2．IRISの拡大解釈

一般的にIRISという概念はHIV感染患者の治療後に生じる症状のみに用いられてきた．しかし，IRISはHIV感染症以外でも，同様の病態がさまざまな状況で起こっていることが分かってきた[4]．HIV感染以外でIRISを生じやすいとされるのは，ステロイドや免疫抑制剤の減量時，あるいは生物学的製剤や化学療法などの中止後である[4]．しかしこのような状況で起こってくる感染症をIRISと診断する際の問題は，HIV感染の際のIRISのようにHAART療法の開始という免疫機能の回復のスタートポイントがはっきりしない点にある．そのポイントとしては，ステロイドや免疫抑制剤の減量あるいは中止がHAART療法の開始時に相当すると考えると，ある程度HIV感染の際と類似した経過で発症する場合が少なくないことが理解できるはずである．このようにHAART療法以外の状況でIRISと診断する際には，どの時点が免疫の回復ポイントになるのかを明確にしておく必要がある．