

Intractable genital ulcers from herpes simplex virus reactivation in drug-induced hypersensitivity syndrome caused by allopurinol

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Abstract

Background Drug-induced hypersensitivity syndrome (DIHS/DRESS) is a severe adverse systemic reaction. Reactivation of human herpesvirus (HHV) family members other than HHV-6 has been reported in patients with DIHS. Reactivation of HHV family members is generally characterized by increased serum antibody titers against the virus. By contrast, clinical symptoms caused by viral reactivation are relatively rare.

Method We report a case of DIHS with intractable genital ulcers from reactivation of herpes simplex virus (HSV) in accordance with reactivation of HHV-6 and cytomegalovirus (CMV).

Result Twenty-two days after the onset of the rash, the patient developed intractable genital ulcers that were resistant to treatment. Histological examination of the ulcers revealed necrotic degeneration in the epidermal cells, with giant cells containing inclusion bodies and marked lymphocytic infiltration in the upper dermis. Immunohistochemical staining with antibodies reactive to HSV or CMV showed that these giant cells were positive for HSV but negative for CMV.

Conclusion Genital herpes is a common skin disease. However, our case was considered to be a DIHS-associated symptom, not an accidental complication, as the symptoms were severe and resistant to treatment.

Introduction

Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is a severe adverse systemic reaction characterized by high fever, facial edema, maculopapular rash and/or erythroderma, generalized lymphadenopathy, atypical circulating lymphocytes, and abnormal liver function tests.¹ Reactivation of human herpesvirus (HHV) family members other than HHV-6 has been reported in patients with DIHS.² Reactivation of HHV family members is generally characterized by increased serum antibody titers against the virus. By contrast, clinical symptoms caused by viral reactivation are relatively rare. In some cases, viral-associated complications, such as cytomegalovirus (CMV)-induced myocarditis, colitis, or pneumonia may occur. In this study, we report a case of DIHS with intractable skin ulcers from reactivation of herpes simplex virus (HSV) in accordance with reactivation of HHV-6 and CMV.

Case report

An 88-year-old Japanese male patient with a history of hyperuricemia was started on allopurinol. He had received spironolactone and furosemide with amlodipine besilate for hypertension as well. Four weeks after taking allopurinol, he developed a fever of 39 °C, with the appearance of a generalized pruritic rash on his face, trunk and extremities. He also developed hyperemic conjunctiva, and allopurinol was discontinued. His laboratory findings showed eosinophilia of 13% and atypical lymphocytes. He suffered from renal dysfunction and his creatinine level was 1.5 mg/dl. Hepatobiliary enzymes were elevated: alanine aminotransferase was 86 IU/l; aspartate aminotransferase was 64 IU/l; alkaline phosphatase was 602 IU/l; and lactate dehydrogenase was 322 IU/l. Three days after discontinuation of allopurinol, he was started on methyl prednisolone 250 mg daily for 3 d, followed by oral prednisolone 20 mg daily. The rash and fever temporarily subsided, but worsened again with

leukocytosis ($10\ 100/\text{mm}^3$) and an exacerbation of hepatobiliary enzymes. After prednisolone was escalated to 30 mg daily, the patient was admitted to Kanazawa University Hospital on day 20. Examination revealed a generalized eruption with purpuric lesions (Fig. 1). There was no lymphadenopathy or hepatomegaly. Twenty-two days after the onset of the rash, he developed intractable genital ulcers that were resistant to treatment (Fig. 2a). Vidarabine ointment was used, but insufficient improvement was achieved. He agreed to a skin biopsy. Biopsy was performed on day 24 and the specimen from the penis revealed necrotic degeneration in the epidermal cells, with giant cells containing inclusion bodies and marked lymphocytic infiltration in the upper dermis (Fig. 2b). Immunohistochemical staining with antibodies reactive to HSV or CMV showed that these giant cells were positive for HSV but negative for CMV (Fig. 2c). The antibody used in the staining had cross-reactivity to HSV-1 and HSV-2. Therefore, this lesion was diagnosed as a genital ulcer caused by HSV. Oral valacyclovir 500 mg daily was given, and genital ulcers were epithelialized 16 d after the initial administration (Fig. 3).

Virological investigations were performed to examine viral reactivation. Samples of the patient's sera obtained 10, 20, 28, 48, and 69 d after the onset of the rash were tested for HSV, Epstein-Barr virus (EBV), HHV-6 and CMV (Table 1). HSV serological tests revealed a rise in



Figure 1 Clinical features on admission. Infiltrative erythematous papules on the trunk

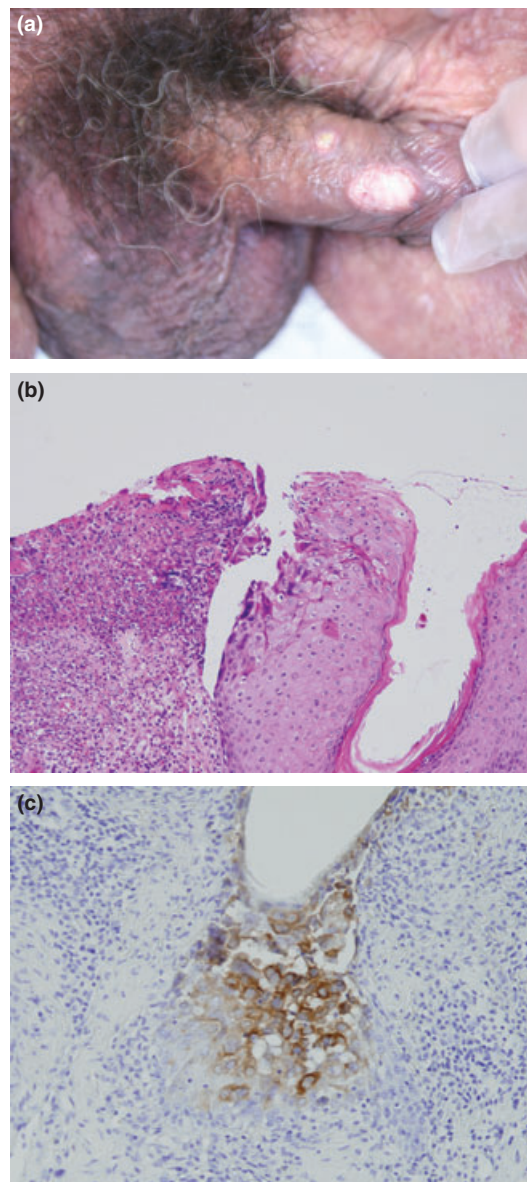


Figure 2 (a) Clinical features of ulcers on the penis. (b) Biopsy specimen from the penis revealing necrosis and reticular degeneration of the epidermis and multinucleated giant cells (hematoxylin-eosin stain), (200 $\times$). (c) Immunohistochemical staining for herpes simplex virus-1, (400 $\times$)

antibody titers; the titers of HSV IgG increased from 74.6 index to >128 index using enzyme immunoassay (EIA) (normal range, <2.0 index) within the following 5 weeks. HHV-6 DNA was detected on day 28 (670 copies/ μg DNA). The titers of HHV-6 IgG were almost stable between 1:160 and 1:320 until day 48, but then increased to 1:640 on day 69. CMV antigenemia was suggested by the direct detection of CMV antigen in the nuclei of peripheral blood leukocytes: 61 CMV pp65

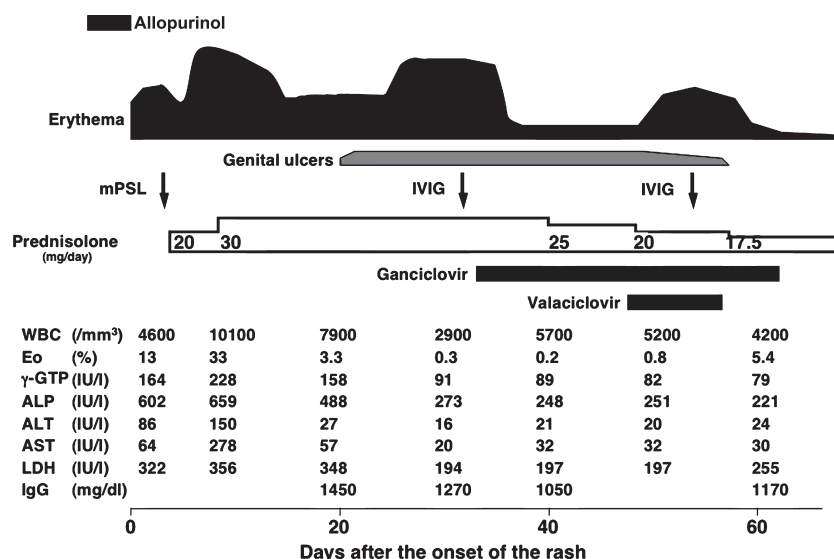


Figure 3 Clinical course of the patient. Day 1 represents the day of onset of skin eruption. IVIG, mPSL, WBC, Eo, γ-GTP, ALP, ALT, AST, LDH, and IgG indicate intravenous injection of immunoglobulin, methyl prednisolone, white blood cell counts, eosinophils (percentage of total white blood cells), gamma-guanosine triphosphate, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and immunoglobulin G, respectively

Table 1 Viral-specific antibody titers

	Day after onset of skin eruption				
	Day 10	Day 20	Day 28	Day 48	Day 69
HSV IgG (EIA)	74.6	ND	33.7	>128	76.4
EBV VCA-IgM (FA)	10	<10	ND	<10	<10
EBV VCA-IgG (FA)	80	80	ND	40	40
HHV-6 IgG (FA)	ND	320	160	320	640
HHV-6 DNA (copy/μg DNA)	ND	0	670	290	32
CMV antigenemia*	ND	1	61	3	0

HSV, herpes simplex virus; EBV, Epstein-Barr virus; VCA, virus capsid antigen; HHV-6, human herpesvirus 6; CMV, cytomegalovirus; EIA, enzyme immunoassay; FA, fluorescent antibody method; ND, not done.

*Number of CMV pp65 antigen-positive cells per 15 000 leukocytes.

antigen-positive cells/15 000 leukocytes on day 28. At that time, the skin rash was exacerbated, and ganciclovir was started. After ganciclovir treatment for 4 weeks, the skin rash improved, and a test for CMV antigen in the blood was negative. Serological tests for EBV showed stable IgG titers and no IgM. Tests for CMV IgG and IgM were not performed.

Discussion

Drug-induced hypersensitivity syndrome is a severe form of drug eruption in which HHV-6 reactivation is considered to be involved.³ Recent reports have suggested that reactivation of other HHVs, such as HSV,⁴ EBV,⁵ CMV,⁶

and HHV-7⁷ could be involved in the development of DIHS as well. Similar sequential reactivation of the herpesvirus family occurs in some cases, as is seen in patients who have undergone bone marrow transplant (BMT). Reactivation of HHV in DIHS is defined as increased titers of viral-specific antibodies, and associated clinical symptoms do not necessarily occur. On the other hand, clinical symptoms of reactivation of the HHV family members, such as herpes labialis and genital herpes from HSV, encephalitis from HHV-6, pneumonia, colitis and retinitis from CMV and herpes zoster from varicella-zoster virus (VZV) are often present in BMT patients, whose immune systems are severely compromised by immunosuppressive therapy. Thus, the difference in the frequency of these clinical symptoms between patients with DIHS and those with BMT might be explained by the degree of immunosuppression in each patient type.

Gastrointestinal bleeding, myocarditis and pneumonia may occur as occasionally fatal CMV-associated symptoms in patients with DIHS. By contrast, only a few cases of herpes labialis from HSV reactivation and herpes zoster from VZV reactivation in patients with DIHS have been reported to date.⁴ Two possibilities are raised to explain the apparent difference in the frequency of clinical recurrence among HHV family members in DIHS. First, the HHV-related eruption seen in DIHS occurs in a hair follicle; thus, it could be missed or misdiagnosed as folliculitis. Second, mechanisms of latent infection and reactivation are different between HSV/VZV and CMV. HSV and VZV establish a latent infection in the sensory ganglion. Viruses are reactivated by immunosuppression or stress. Some viruses may travel along the axons anterogradely to reach the skin and generate small blisters on

the skin.⁸ On the contrary, monocyte and/or granulocyte progenitor cells of the bone marrow are major sites of CMV latency.⁹ It is considered that, under immunocompromised conditions, proliferation of CMV in monocytes can cause viremia and CMV infection of various cells, including endothelial cells, leading to various internal organ complications. These differences in the mechanisms of latency and reactivation may in part explain the distinction of the frequency in clinical presentation. Genital herpes is a common skin disease. Our case was considered to be a DIHS-associated symptom from HSV reactivation, not an accidental complication, as the symptoms were severe and resistant to treatment. However, we cannot exclude the possibility that the genital ulcers might be initially caused by HSV but became refractory to treatment as a result of coinfection with CMV, as leukocytopenia is a sign suggesting CMV reactivation and CMV antigenemia was detected on day 28. Additionally, increased viral specific antibody titers shown in Table 1 might be influenced by the intravenous immunoglobulin (IVIG) treatment, which may have contained high titers of antibodies against HHV.

Apart from the exacerbation of genital herpes by reactivated HSV, our case demonstrates the importance of careful monitoring of CMV reactivation in DIHS. It is essential to accurately diagnose active CMV infection, as it may often cause severe refractory rash and mortality in DIHS.¹⁰ The best approach for this is the direct detection of CMV antigen in the nuclei of peripheral blood leukocytes with the pp65 direct antigenemia test. The accumulation of pp65 antigen appears before the translation of CMV immediate-early protein and viral replication,¹¹ and the presence of positive pp65 cells was associated with a high risk of developing CMV disease.¹² In our case, CMV antigenemia detected by a pp65 test was associated with skin rash exacerbation, and ganciclovir, not an increase in corticosteroid, was effective to improve the rash. Thus, it appears reasonable to conclude that monitoring the number of positive pp65 leukocytes in DIHS is a useful and essential approach for accurate and early detection of CMV reactivation.

Allopurinol, an analog of hypoxanthine, has been widely used in clinical practice for the treatment of hyperuricemia and gout. Allopurinol is generally well tolerated, but it is reported that approximately one in 260 patients treated with allopurinol can suffer from allopurinol-induced DIHS.¹³ As renal dysfunction and/or use of diuretics are considered to be at great risk for developing allopurinol-induced toxicity,¹⁴ it is likely that his decreased renal function and/or diuretic medications could be provocative factors to evoke allopurinol hypersensitivity in our case. Although the exact mechanisms of the pathophysiology of antiviral resistance in the patients with

DIHS are unknown, several possibilities have been raised. First, administration of allopurinol may modulate modulating B cell and T cell immune response.¹⁵ Second, patients with DIHS showed a reduction in the serum IgG concentration at the onset of DIHS, accompanied with a decrease in the number of B cells and NK cells.¹⁶ This appears intriguing because NK cells can induce the differentiation of B cells to immunoglobulin-producing cells.¹⁷ Third, recent studies have demonstrated that regulatory T cells (Tregs) are increased in only acute phase of DIHS¹⁸ and that Tregs suppress the antibody production by inducing apoptosis of B cells.¹⁹ It is likely that these factors can contribute to the development of DIHS with mutual involved. However, whether these effects are specific for allopurinol or in general for other drugs is not fully elucidated. More studies will be required to clarify these issues.

Accumulating evidence suggests that IVIG therapy is a potential candidate to treat the patients with DIHS.^{20,21} IVIG may counteract the immune response either by down-regulating the abnormal T cell activity or by blocking antibodies²⁰ although the precise mechanism of IVIG treatment remains unknown. To overcome this recalcitrant reactivation of HHV in the patients with DIHS, an adjunctive therapy of IVIG to antiviral agent may be effective.²² Further investigations are needed to establish effective therapies for DIHS and complicated intractable viral infections.

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