

Single Case

A Case of Salazosulfapyridine-Induced Hypersensitivity Syndrome in a Rheumatoid Arthritis Patient with Relapse of Skin Erythema

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Keywords

Drug-induced hypersensitivity syndrome · Human herpesvirus 6 · Cytomegalovirus · Salazosulfapyridine · Relapse

Abstract

We experienced a rare case of drug-induced hypersensitivity syndrome (DIHS) in which salazosulfapyridine (SASP) reactivated human herpesvirus 6 (HHV-6) and cytomegalovirus (CMV), which resulted in a relapse of skin symptoms after changing to mizoribine. At the time of recurrence of skin erythema after the initiation of mizoribine, the serum DNA titers of not HHV-6 but CMV were elevated. A drug-induced lymphocyte stimulation test was negative for mizoribine but positive for SASP. In this case, DIHS developed with SASP in association with HHV-6 and CMV reactivation. The immunocompromised state induced by herpes virus reactivation and mizoribine might have caused the relapse of skin erythema.

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Introduction

Drug-induced hypersensitivity syndrome (DIHS) is an allergic reaction characterized with skin rash, fever, and organ involvement [1]. DIHS is known to present a long-term illness with frequent relapses and recurrences over weeks or months even after treatment discontinuation.

We experienced a case of DIHS with human herpesvirus 6 (HHV-6) and cytomegalovirus (CMV) reactivation by salazosulfapyridine (SASP). Skin erythema subsequently relapsed after switching to mizoribine. Therefore, we would like to report the case and discuss the possible mechanism underlying relapse of skin erythema.

Case Report

A 61-year-old Japanese man developed pyrexia of $>38^{\circ}\text{C}$, anorexia, stomach fullness, decreased saliva secretion, diarrhea, and generalized erythema 2 weeks after the initiation of SASP as treatment for rheumatoid arthritis. He received one steroid infusion and the withdrawal of SASP. He was referred to our hospital 4 days after the onset of his symptoms. In addition to slight pyrexia and neck lymphadenopathy, military-sized red papules and erythema expanded over the whole body (Fig. 1a). A laboratory analysis showed leukocytosis ($10,400/\text{mm}^3$) with 5.0% atypical lymphocytes and 1.0% eosinophils, and elevated liver enzymes (aspartate aminotransferase, 140 IU/L; alanine aminotransferase, 221 IU/L). The anti-HHV-6 IgG titer increased from 20 (Day 0) to 640 (Day 23). IgG titers of herpes simplex virus, Epstein-Barr virus, mycoplasma virus, HHV-1, CMV, varicella zoster virus, HHV-7, and measles virus were not significantly elevated. A leg skin specimen showed lymphocytic exocytosis, liquefaction degeneration, and infiltration of both lymphocytes and histiocytes in the upper dermis (Fig. 1b). A drug-induced lymphocyte stimulation test was positive for SASP. We diagnosed this patient with DIHS by SASP. Pyrexia and abdominal symptoms improved immediately after the withdrawal of SASP and erythroderma gradually disappeared with topical steroid application (Fig. 1c).

Erythroderma recurred 4 days after switching to mizoribine 2 weeks after the skin eruption disappeared (Fig. 1d). Erythroderma disappeared 1 week after the discontinuation of mizoribine. The anti-HHV-6 IgG titer in the recurrence of skin erythema after the initiation of mizoribine (day 34; 320) was lower than that in first skin erythema resolved (day 23; 640). However, the CMV DNA levels at day 34 were elevated (4.7×10^2 copies/mL) compared to those at day 0 (1.0×10^2 copies/mL) and at day 23 (2.2×10^2 copies/mL). The serum IgG and TNF α were not changed. Drug-induced lymphocyte stimulation test was negative for mizoribine. After the erythema disappeared, mizoribine was re-administered; however, there was no recurrence.

Discussion and Conclusions

Several studies demonstrated that herpesviruses including HHV-6 reactivation are associated with the onset and maintenance of DIHS [2]. Aota and Shiohara [3] found that regulatory T cells proliferated during the acute phase of DIHS, suggesting that the suppression of antiviral immunity by regulatory T cells might induce the reactivation of HHV-6. Tohyama et al. [4] investigated that there was no significant difference between patients with elevated

HHV-6 antibody titers and patients with normal antibody titers in the relapse of skin rash with DIHS. CMV reactivation in DIHS occurs 1–2 weeks after HHV-6 reactivation [5]. We experienced DIHS with HHV-6 and CMV reactivation, and the CMV DNA level in the relapsed rash after switching to mizoribine was elevated. In this case, we hypothesized that the relapsed skin rash had been induced under a state of immunosuppression with mizoribine and CMV reactivation. If we experience similar cases in the future, in addition to virological examinations, we need to examine serologically immunosuppression such as regulatory T cells, and to also administer systemic treatments including steroids and antiviral agents.

Statement of Ethics

Informed consent was obtained from the patient. The study complied with the Declaration of Helsinki.

Disclosure Statement

The authors declare no conflict of interest.

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None.

Author Contributions

We all are responsible and in agreement with the content and writing of the manuscript to which we all contributed significantly.

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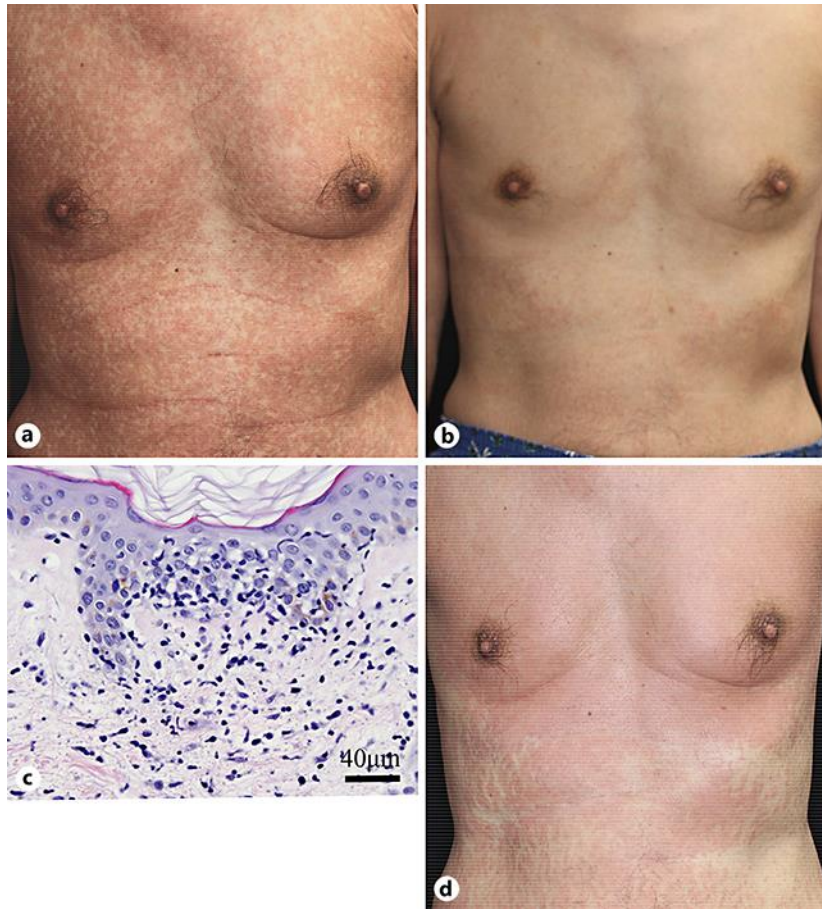


Fig. 1. The clinical features and histological findings. **a** The clinical features at the first visit. Symmetric erythema was distributed over the whole body. Mucosal areas, such as the oral cavity and penis, were not involved. **b** Clinical features at 1 month after discontinuing salazosulfapyridine. The patient's erythema almost remitted with topical steroid treatment. **c** The histopathological features at the first visit. Hematoxylin-eosin staining of a skin biopsy with erythroderma. Bar indicates 40 µm. **d** The patient's erythema relapsed 4 days after changing to mizoribine.