

SHORT COMMUNICATION

Drug-induced Hypersensitivity Syndrome in Association with Varicella

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Drug-induced hypersensitivity syndrome (DIHS) is a severe multiorgan reaction related to the reactivation of human herpesvirus (HHV)-6 (1). Recently, the involvement of other types of HHV, including herpes simplex virus (HSV), Epstein-Barr virus (EBV), HHV-7, and cytomegalovirus (CMV), has been reported (2–5). We report here the first case of DIHS possibly associated with reactivation of varicella-zoster virus (VZV).

CASE REPORT

A 72-year-old woman was referred to our clinic because of skin eruptions covering almost her entire body. About 4 weeks before, she had taken salazosulphapyridine, bucillamine, and prednisolone (PSL) for treatment of rheumatoid arthritis. However, she stopped taking the drugs one week before referral due to vomiting and diarrhoea. She had a slight fever and generalised skin lesions for 3 more days. She was first hospitalised in the local hospital with a primary diagnosis of drug eruption. Thirty mg/day of PSL was administered intravenously on the first day of hospitalisation. However, there was no improvement in symptoms and she was referred to our clinic. Her vitals on admission were as follows: temperature of 37.2°C and blood pressure of 185/82 mmHg. Physical examination revealed infiltrative erythematous macules and papules on the entire body and facial oedema (Fig. 1a). There was no lymphadenopathy. Laboratory data were as follows: white blood cell (WBC) count of 11,200/mm³ with 65% neutrophils, 23% lymphocytes, 4% eosinophils, 0% monocytes and C-reactive protein of 3.2 mg/dl (normal <0.20 mg/dl). Liver and renal functions were within normal limits.

A skin biopsy specimen obtained from the left thigh revealed focal spongiosis and basal vacuolar change with lymphocyte exocytosis in the epidermis and superficial perivascular lymphocytic infiltration in the dermis. We suspected drug eruption

including a possibility of DIHS because of the prescription of salazosulphapyridine. We prescribed 60 mg/day of oral PSL. We consulted the department of internal medicine regarding gastrointestinal symptoms. She was diagnosed with acute colitis associated with drug eruption and was recommended treatment with antiflatulent and no fasting temporarily. Since the skin lesions and fever were improved, we gradually tapered the daily dose of PSL and terminated administration after 15 days.

However, on the 17th day after onset of the first rash, she developed erythemas and papules on the abdomen again with high fever of 38.0°C and she showed abnormal values in liver function tests: aspartate aminotransferase (AST) level, 70 IU/l (normal 13–33 IU/l); alanine aminotransferase (ALT) level, 280 IU/l (normal 8–42 IU/l); gamma-glutamyltransferase (γ -GT) level, 66 IU/l (normal 10–47 IU/l); lactate dehydrogenase (LDH) level, 329 IU/l (normal 119–229 IU/l). Ten days later, though WBC count was normalised to 5,500/ μ l, eosinophilia of 22% occurred. A second skin biopsy from the patient's abdomen revealed marked spongiosis with lymphocyte exocytosis, extravasated erythrocytes in the epidermis and severe basal vacuolar change (Fig. 1b). Meanwhile, multiple umbilicated vesicles were also seen sporadically all over her body on the 17th day after onset of the first rash (Fig. 1c). The Tzanck test showed multinucleated and ballooning cells. A diagnosis of varicella was made. Her previous history of varicella was unclear.

She was treated with aciclovir intravenously for one week and the vesicles promptly healed with crusts. The erythemas also gradually improved only with topical steroid treatment for 2 weeks. Although endoscopy on day 37 revealed an irregular and deep cecal ulcer, serum CMV antigen was negative. The ulcer improved and became scarred after 4 months.

Samples of the patient's sera obtained on the 7th, 22nd and 37th days after onset of the first rash were tested for VZV, HHV-6,

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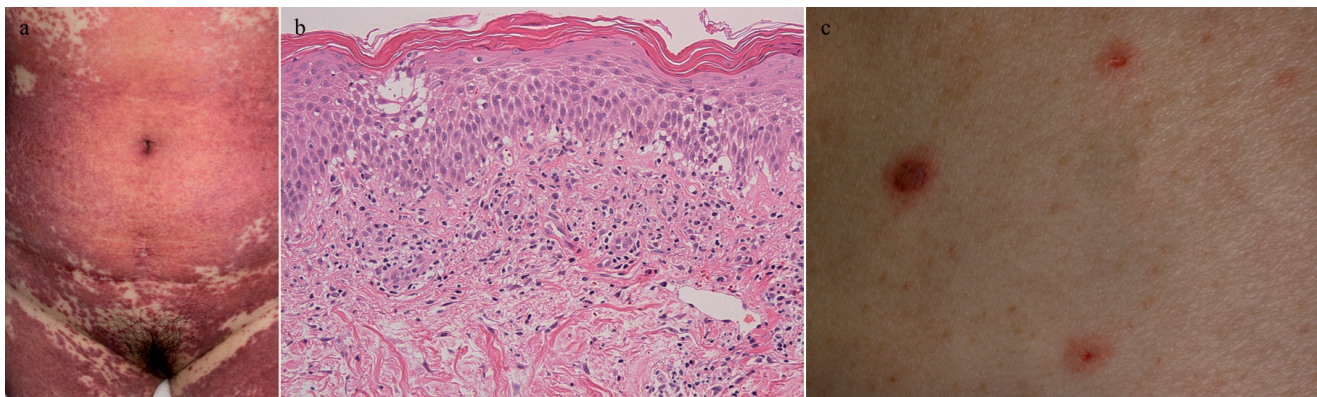


Fig. 1. Clinical features on admission. Infiltrative erythematous macules and papules were seen on the entire body (a). A second skin biopsy from the abdomen revealed marked spongiosis with lymphocyte exocytosis, red blood cells in the epidermis and marked basal vacuolar change (haematoxylin-eosin stain) ($\times 100$) (b). Umbilicated vesicles all over the body sporadically (c).

HHV-7, EBV, and CMV (Table S1¹). Notably, reactivation of VZV was confirmed. Furthermore, reactivation of HHV-6 was followed by reactivation of HHV-7 and CMV. There was no significant change in specific IgG titre for EBV. We measured the patient's serum immunoglobulin levels on the 22nd and 37th days and they were approximately within normal ranges. Drug lymphocyte-stimulation tests were performed on the 7th day, with a positive result for salazosulphapyridine (stimulation index, 190%; reference value, <180%). These findings fulfilled a diagnostic criteria of DIHS (atypical DIHS) (6).

DISCUSSION

DIHS is a severe adverse drug-induced reaction. It is characterised by a delayed onset, variable clinical symptoms and a prolonged disease course (7). It should be noted that DIHS is a complex disease consisting of drug allergy and viral infection, specifically HHV-6 infection. Recently, accumulating evidence suggests that other HHVs, such as HSV, EBV, HHV-7 and CMV might be reactivated during the course of DIHS (2–5).

It has been suggested that there are close similarities between DIHS and graft-versus-host disease (GVHD) (8). In addition, Shiohara et al. (9) reported that DIHS is a manifestation of immune reconstitution syndrome (IRS). IRS was originally defined as a paradoxical deterioration in clinical status attributable to the recovery of immune response in HIV patients receiving highly active antiretroviral therapy (HAART) (10). Based on the concept of IRS, various opportunistic infectious diseases occur or recur on a reducing dose or withdrawal of immunosuppressive agents such as PSL (9).

The most critical complications in the course of DIHS are symptoms induced by reactivation of CMV such as cutaneous and gastrointestinal ulcers, gastrointestinal bleeding, myocarditis and pneumonia. In addition, rare but severe complications of DIHS are encephalitis and type 1 diabetes mellitus caused by HHV-6 (11).

There have been a few reports of complications due to reactivation of HSV or VZV in DIHS as seen in our case (8). Hamaguchi et al. (2) suggested that differences in the mechanisms of latency and reactivation may in part explain the difference in the frequency of clinical recurrence of DIHS among HHV family members.

VZV infection is frequently observed in the course of IRS (12). The infection commonly manifests as cutaneous dissemination and occasionally leads to fatal complications. There have only been 3 reports on herpes zoster in the course of DIHS (13). Kano et al. (13) suggested that the reduction or withdrawal of corticosteroid in the setting of DIHS could contribute to the development of herpes zoster. However, there has been no report of varicella as a DIHS complication. Our case was considered to be a DIHS-associated symptom of VZV reactivation, because she had been in her home or in the hospital 3 weeks before the appearance of the vesicles.

It is well known that the cascade of virus reactivation initiated by HHV-6 or EBV extends to HHV-7 and eventually to CMV (8).

Fortunately, our patient had only mild symptoms of varicella. However, the prognosis of varicella or herpes zoster in the course of DIHS remains unclear. It is important for clinicians to be aware of the possibility of varicella or herpes zoster complicated by DIHS.

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