Successful Treatment for Toxic Epidermal Necrolysis/Drug-Induced Hypersensitivity Syndrome Overlap with Corticosteroids, Intravenous Immunoglobulins and Plasma Exchange

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Abstract

An 80-year-old woman treated with allopurinol showed atypical target lesions with blister and erosions, which rapidly extended over the trunk and limb. She was diagnosed as Toxic Epidermal Necrolysis (TEN). Despite the treatment with pulsed corticosteroids and i.v. immunoglobulins, the skin lesions rapidly extended over the entire body. Strikingly, the progression of blistering was stopped by Plasma Exchange (PE). Since human herpes virus 6 reactivation occurred, she was also diagnosed as Drug-Induced Hypersensitivity Syndrome (DIHS). We presented here a rare case of DIHS with skin manifestation of TEN successfully treated with PE.

Introduction

Drug-induced hypersensitivity syndrome (DIHS), also referred to as drug reaction with eosinophilia and systemic symptoms (DRESS), is a severe systemic hypersensitivity reaction caused by specific drugs such as anticonvulsants and allopurinol [1,2]. It is characterized by late disease onset, fever, rash, hepatic dysfunction, hematological abnormalities, lymphadenopathy with reactivation of human herpes virus such as herpes virus 6 (HHV-6), Epstein-Barr virus and cytomegalovirus (CMV) [2]. On the other hand, toxic epidermal necrolysis (TEN) is a life-threatening, drug-induced disorder characterized by extensive epidermal necrosis and mucous membrane involvement [3]. Here, we report a rare case of DIHS with skin manifestation of TEN, diagnosed as TEN/DIHS overlap, which was successfully treated with plasma exchange (PE).

Case Report

An 80-year-old Japanese woman had been treated with allopurinol 100 mg daily for hyperuricemia. On day 30 of the treatment she became feverish and developed widespread erythematous macules with blisters and oral erosions (Figure 1a and 1b). Epidermal detachment was observed over 30% of the body surface area. Ocular involvement was not shown. Biopsy specimens from erythema on her abdomen revealed liquefaction degeneration at the epidermal-dermal junction with many necrotic keratinocytes and perivascular cell infiltrates in the upper dermis (Figure 2a and b). She was diagnosed as TEN. Abnormal laboratory findings were as follows: white blood cells, 4.3x10³ µL⁻¹ (reference range [RR], 3.0-8.5 µL⁻¹ (eosinophil, 0.2-7.3 %); AST, 39 IUxL⁻¹ (RR, 13-33 IUxL⁻¹); ALT, 106 IUxL⁻¹ (RR, 6-27 IUxL⁻¹); γ-GPT, 485 IUxL⁻¹ (RR, 5-40 IUxL⁻¹); alkaline phosphatase, 1015 IUxL⁻¹ (RR, 104-338 IUxL⁻¹); lactate dehydrogenase, 425 IUxL⁻¹ (RR, 119-229 IUxL⁻¹); C-reactive protein, 6.3 mgxdl⁻¹ (RR, <0.3 mgxdl⁻¹); anti-HHV-6 IgG antibody titer, x40 (RR, <x10); CMV IgG, 34.1(RR, <2.0).

Figure 1a, b: Widespread dark-red erythematous macules with blisters and erosions on her face and back

Figure 2a, b: Liquefaction degeneration at the epidermal-dermal junction with many necrotic keratinocytes and perivascular infiltrating cells in the upper dermis (x100, x200, respectively)
Firstly, she was treated with pulse therapy of glucocorticoid consisting of intravenous (i.v.) methylprednisolone at a daily dose of 1 g for 3 days, and i.v. immunoglobulins (IVIg) (25 g/day for 5 days), followed by oral administration of prednisolone at 60 mg/day. However, her skin lesions did not show improvement, but the lesions rapidly extended over the entire body. Accordingly, we decided to treat her with plasma exchange (PE). Plasma exchange was performed three times using Apheresis monitor KM-8900 ® (Kawasumi Laboratories, INC, Tokyo, Japan). Plasma was separated from the blood cells by Plasmacure PE® (Kawasumi Laboratories, INC, Tokyo, Japan). On each exchange, about 2.6L of plasma was removed. The replacement of fluid consisted of about 2 L of fresh frozen plasma to supply lost plasma including coagulation factors. Strikingly, Blistering with extensive epidermal necrosis halted on the second day of PE and there was rapid re-epithelization in nine days of introduction of PE (Figure 1c and 1d). Meanwhile, the diagnosis of DIHS was also made, since the HHV6 DNA copy number was 30,000 copies/µg DNA in the peripheral blood assessed by quantitative real-time PCR at the 14 day of the onset of the rash, and the anti-HHV-6 IgG antibody titer was x5120 at 18 day, confirming that the HHV-6 reactivation occurred in this patient. In addition, the serum titers of CMV IgG were also increased (>100). We diagnosed this case as TEN/DIHS, and speculated that the causative drug was allopurinol, which is frequently associated with DIHS.

Discussion

The diagnosis of DIHS is not made by specific eruptions, but by based on its characteristic clinical course such as multiple organ dysfunction and series of reactivation of herpes viruses, specifically HHV-6. The skin manifestations of DIHS include maculopapular rash, erythema multiforme, exfoliative dermatitis, acute generalized exanthematous pustulosis, and erythema multiforme. The skin manifestation of TEN include a bullae, erosions and necrosis at the mucosal membranes, which are early signs of TEN. The specific eruptions may be confused with bullous pemphigoid and erythema multiforme, but TEN is a systemic disease which includes multiple organ involvement.

Recently, a few cases with TEN/DIHS overlap have been reported [4-7]. Teraki et al. reported TEN due to zonisamide associated with reactivation of HHV-6 [4]. They mentioned that HHV-6 reactivation has not been reported in patients with SJS/TEN and their cases were exceptional. However, their patients might be diagnosed as TEN/DIHS overlap. Viera et al. also reported that phenytoin-associated hypersensitivity syndrome with features of DRESS and TEN/SJS [5]. Recent study demonstrated severe cutaneous adverse reactions to drugs (SCARs) including SJS/TEN, DIHS/DRESS and acute generalized exanthematous pustulosis (AGEP) [8].

We emphasize that SJS/TEN due to causative drugs for DIHS such as anticonvulsants may recapitulate DIHS, which shows prolonged clinical course due to relapse with successive reactivation of human herpes viruses; therefore, overlapping with DIHS might affect the specific features of SJS/TEN.

References


