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 a 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, 22.5 % RR, 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.

![Figure 1c, d: Improvement of skin lesions at 9 days after PE](image)

**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 pustular dermatosis-like eruptions and erythroderma, and rarely, Stevens Johnson syndrome (SJS)/TEN. The clinical findings in our case fulfilled the diagnosis criteria for both TEN and DIHS.

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], could overlap; in that overlapping was found in 3 out of 145 cases with SCARs. One was an overlapping of AGEP and DIHS/DRESS and the other two cases were SJS/TEN and DIHS/DRESS. They suggested that the diagnostic algorithms helped reliable discrimination among AGEP, DIHS/DRESS and SJS/TEN.

Takahashi et al. showed that dramatic expansion of functional regulatory T (Treg) cells was found in the acute stage of DIHS [9]. In contrast, Treg function was profoundly impaired in TEN, while Treg number was not impaired. Since skin homing receptors expressed on Treg cells were abundant in patients with DIHS than in TEN, Treg cells preferentially accumulated in the skin lesions of DIHS. They speculated that transient impairment in Treg function during the acute stage of TEN might be related to severe epidermal damage. Although we could not examine the distribution and function of Treg cells in our case, it is interesting how Treg function might be altered during the development of TEN/DIHS.

The mortality rate of TEN is approximately 30% mainly due to systemic infection. The most important prognostic factors are age and the extent of skin involvement. Although our patient was an old woman, who showed epidermal detachment over 30% of the body surface area, we gave her a successful therapy to cure. Since drug-specific T cells are generally thought to be responsible for the epidermal damage at the early stage of TEN, a high dose of systemic corticosteroids, IVIg, and immunosuppressive drugs such as cyclophosphamide or cyclosporine have been used. However, specific treatment for TEN has not been established. Plasmapheresis (PP), including PE and double-filtration PP (DFPP), has been reported to be effective in several cases of TEN from the middle 1980s. Indeed, PP therapies led to dramatic and rapid improvement of clinical symptoms in severe and refractory TEN patients [10,11]. Narita et al. mentioned that PE was more efficacious against TEN than DFPP, although they both helped improve the imbalance of immune responses in TEN [11]. Previous study demonstrated that short time effectiveness of apheresis for Guillain-Barré syndrome was superior in PE to DFPP [12]. Although it is not clear why the short-term therapeutic effect of PE is superior to that of DFPP, one reason may be that, while PE removes whole plasma without specificity, DFPP selectively extracted large molecule substances from plasma. The other previous study showed that PE decreased the immunoglobulin (Ig) G concentration more than DFPP [13]. Since the precise pathogenesis of TEN is not clear, the therapeutic mechanism of PP remains unclear. While our case showed rapid improvement by introduction of PE, corticosteroids and IVIg might synergistically enhance its effect to improve immunological abnormalities.

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**


