Successful Combination Therapy Including Plasma Exchange for Severe Toxic Epidermal Necrolysis

Takashi Watari, MD, DTMH,1 Shuku Sato, MD,2 Haruki Uojima, MD,3 and Yasuharu Tokuda, MD, MPH4

1 Postgraduate Clinical Training Center, Shimane University, Shimane, Japan
2 Department of Hematology, Shonan Kamakura General Hospital, Kanagawa, Japan
3 Department of Gastroenterology, Kitasato University, Kanagawa, Japan
4 Japan Community Healthcare Organization, Tokyo, Japan

Toxic epidermal necrolysis (TEN) is a rare life-threatening disorder. Although its treatment is not standardised due to the unknown pathogenesis and the lack of randomized clinical trials, systemic corticosteroids, immunoglobulins (IVIG) and immunosuppressive drugs such as cyclophosphamide have been used in the treatment of TEN with some success. We present a case with severe TEN treated successfully with combination therapy including plasma exchange. Although it is expensive and requires venous access, use of plasma exchange may be an effective measure leading to rapid cessation of dermal necrolysis, by the removal of inflammatory cytokines, autoantibodies, immune complex or other unknown toxic substances.

Keywords: toxic epidermal necrolysis, Stevens-Johnson syndrome, plasma exchange

Introduction

Both Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe blistering diseases with high mortality.1 These are usually caused by severe cutaneous adverse reaction to drugs. TEN is characterized by epidermal detachment of >30% of the total body surface area, while Stevens-Johnson syndrome affects <10% of the body surface. The involvement of 10–30% of body surface area is called SJS/TEN overlap.2 Diagnosis of these illnesses relies mainly on clinical findings together with the histological analysis of skin biopsy showing epidermal necrolysis due to extensive keratinocyte apoptosis.3 Despite paucity of robust evidence, its suggested treatment include high-dose systemic corticosteroids, high-dose intravenous immunoglobulins, immunosuppressive drugs, or plasmapheresis in addition to supportive care including immediate discontinuation of the offending drug, temperature control, skin care, fluid and electrolyte management, nutrition support, and pain control in burn units or equivalent facilities.4–7 We report a case of severe TEN treated...
successfully with combination therapy including plasma exchange.

Case Report
A 37-year-old Japanese woman with a regular intake of over-the-counter (OTC) medications was admitted to our hospital with acute onset of high fever, sore throat, painful eyes, dry cough, generalized erythematous and purpuric macular rash for several days. Although she had no significant past medical history or social history, she had taken a cold medicine and herbal medicine for common cold and diarrhea in four weeks. On examination, vital signs were blood pressure 130/90 mmHg, heart rate 130/minute, respirations 35/minute, temperature 38.5°C, SpO2 95% while breathing nasal cannula of 4 L/min oxygen. There was conjunctivitis and turbid corneal in the bilateral eyes, ulceration of the mouth, and swollen lip. There were fine crackles bilaterally on lung auscultation. She had generalized skin erythema and irregularly shaped itchy purpuric macules (Figure 1). Other physical findings were non-significant.

Laboratory examination revealed mild leukocytosis without eosinophilia, elevated bilirubin, liver enzyme, KL-6, and C-reactive-protein. Renal function was normal. Anti-nuclear antibodies, antibody of Mycoplasma, viral serology (Mumps, Measles, Herpes Viruses, Human Immunodeficiency Virus, Cytomegalovirus, hepatitis virus, etc), and BP180 antibody were all negative. She underwent skin biopsy on admission and was diagnosed with Stevens-Johnson syndrome with drug-induced interstitial pneumonia (Figure 2).

She started intravenous methyl prednisolone 500 mg/day (Figure 3). The patient was isolated to reduce the risk of secondary infection, and she received fluid and nutrition therapy with high protein content via a nasogastric tube. Consultations with a dermatologist, a plastic surgeon, an ophthalmologist, an otolaryngologist, and a pulmonologist were conducted. On day 3, there was no remarkable improvement with conventional corticosteroid treatment, with extensive epidermal exfoliation covering over 30% of her body surface area on diagnosis of TEN, and worsening respiratory failure (Figure 4). By clinical judgment of the lack of response to corticosteroid therapy, plasma exchange was initiated for three days, while she was intubated and ventilated.
After three sessions of plasma exchanges, exfoliation decreased and extensive reepithelization occurred by day 9 (Figure 5). IVIG (0.3 mg/kg/day) was also added for three days for treatment of respiratory failure. The accompanying pictures show re-epithelization occurring from severe epidermal exfoliation. On day 38, she was discharged home.

Discussion

Drug induced toxic epidermal necrolysis is a rare but potentially lethal disease of the skin and mucous membranes of unknown etiology. Standard therapy has been suggested, including meticulous wound care, fluid replacement, and nutritional support in intensive care setting.8 If it is possible, admission to a specialized Burns Centre is ideal,9 according to 2 cohorts exclusively managed within a Burn Centre in Singapore10 and Hong Kong.11 However, it is difficult to determine whether their outcomes would be better for burn center care because of the higher level of specialist and nursing care available, or they would be worse because these were likely to have been sicker patients.

Conversely, systemic corticosteroids and IVIG are not well established due to the unknown pathogenesis of this illness and the lack of randomized clinical trials.12–15 The main reason of it is that a limited number of patients reduce the reported therapeutic
strategy and its actual effectiveness has to be evaluated in many more patients.\textsuperscript{16} However, there is common agreement considering that TEN as a manifestation of a deregulated immune reaction against epithelial cells.\textsuperscript{17–19} During the first stages of TEN, apoptosis mediates keratinocyte death with a pivotal role of the activated cytotoxic mediators such as Fas-FasL, granulysin, TNF-alpha and above inflammatory cytokines, autoantibodies, and immune complexes might be removed by plasma exchange.

The immune response may be triggered by the interaction between antigen presenting cell which is thought to be keratinocyte in SJS/TEN. Keratinocyte apoptosis is induced by immune synapse between drug, HLA, and T-cell receptor in SJS/TEN. It is considered that a pivotal role of the activated cytotoxic mediators such as Fas-FasL, granulysin, TNF-alpha and above inflammatory cytokines, autoantibodies, and immune complexes might be removed by plasma exchange.

Use of plasma exchange is a relatively safe intervention in the more severe form of TEN,\textsuperscript{28,29} because the above inflammatory cytokines, autoantibodies, immune complexes that are shown or other unknown toxic substances cannot be removed by dialysis.\textsuperscript{30,31} From epidemiological studies of TEN throughout Japan from 2005 to 2007,\textsuperscript{17} three combination therapies like in this case were used in 6 cases in a total 81 cases of TEN. Plasma exchange is now only used as a last resort in TEN patients who are not responding to the standard therapy, including high doses of corticosteroids.\textsuperscript{17,32,33}

Taken into consideration of high expenses for apheresis together with a small number of the patients, the other countries face to difficulty of choice therapy. Hence, it may be hard to conduct a large-scale clinical trial. It remains unknown, therefore, whether plasma exchange alone could effectively treat severe inflammation in TEN. Plasma exchange has some demerits, such as the need of central venous access, the risk of transmission of unknown viruses through the use of fresh frozen plasma (FFP), and very high cost. However, plasma exchange may be possible for plasma exchange to be effective for rapid cessation of dermal necrolysis.

Acknowledgments

We thank Dr. Hiromichi Yamada (International Goodwill Hospital, Yokohama City) for providing the advice and his technical assistance of Fas/FasL. And we also thank Dr. Sumi Hidaka, Dr. Takayasu Ohtake, and Dr. Shuzo Kobayashi for their helpful support.

The authors state that they have no Conflict of Interest (COI).

References


27 Chung WH, Hung SI: Genetic markers and danger


