

LETTER

Cytokine storm arising on the ocular surface in a patient with Stevens—Johnson syndrome

Stevens—Johnson syndrome (SJS) and its more extreme variant, toxic epidermal necrolysis (TEN), are acute, adverse systemic reactions that can affect anyone who takes medications. SJS/TEN predominantly affects the skin and mucosal membranes and predisposes patients to life-threatening complications such as sepsis, respiratory dysfunction and multi-organ failure. Even when a patient does survive this disease, serious ocular discomfort and morbidity often persists life long.^{1 2}

In May 2008, a 59-year-old female inpatient had a case of red eyes, and 2 days later she presented with a sudden onset of high fever and eruption and erosion in the mucocutaneous regions including the mouth, paronychia and bilateral conjunctivitis. Slit-lamp examination revealed a large epithelial defect of the conjunctiva with severe hyperaemia in both eyes (figure 1A,B). There was no viral or bacterial infection, and skin biopsy specimens of the erythematous macules revealed necrotic keratinocytes and liquefaction, compatible with the diagnosis of SJS. Steroid pulse therapy and intensive topical betamethasone (0.1%, 10 times daily) were then initiated (figure 2).

To date, the pathogenesis of SJS/TEN is yet to be fully elucidated, although previous studies have reported that several cytokines may play a role in the accelerated apoptosis or the ocular surface inflammation.^{3 4} To examine the immunological conditions existing in this patient, we measured various cytokine levels in her tear fluid and serum using a Cytometric Beads Array system. This new system makes it possible to simultaneously measure the various cytokines and chemokines using a trace amount (1 µl) of tears in a bead-based immunoassay.

Among the various cytokines measured, the levels of interleukin (IL)-6, IL-8 and monocyte chemoattractant protein-1 (MCP-1), but not IL-1β, IL-5, eotaxin, interferon-γ or macrophage inflammatory protein-1α (MIP-1α), were dramatically increased in this patient's tear fluid and serum (figure 2). Many neutrophils were observed in the smear of the discharge from the ocular surface of this patient, compatible with the results of the tear cytokine measurement (online supplementary figure). The levels of all three cytokines in her tear fluid were extremely high compared with those in her serum at any time point. While upregulated serum cytokines decreased after the corticosteroid pulse, the levels of these cytokines in her tear fluid remained high during the second week despite systemic steroid administration and intensive topical betamethasone. This study

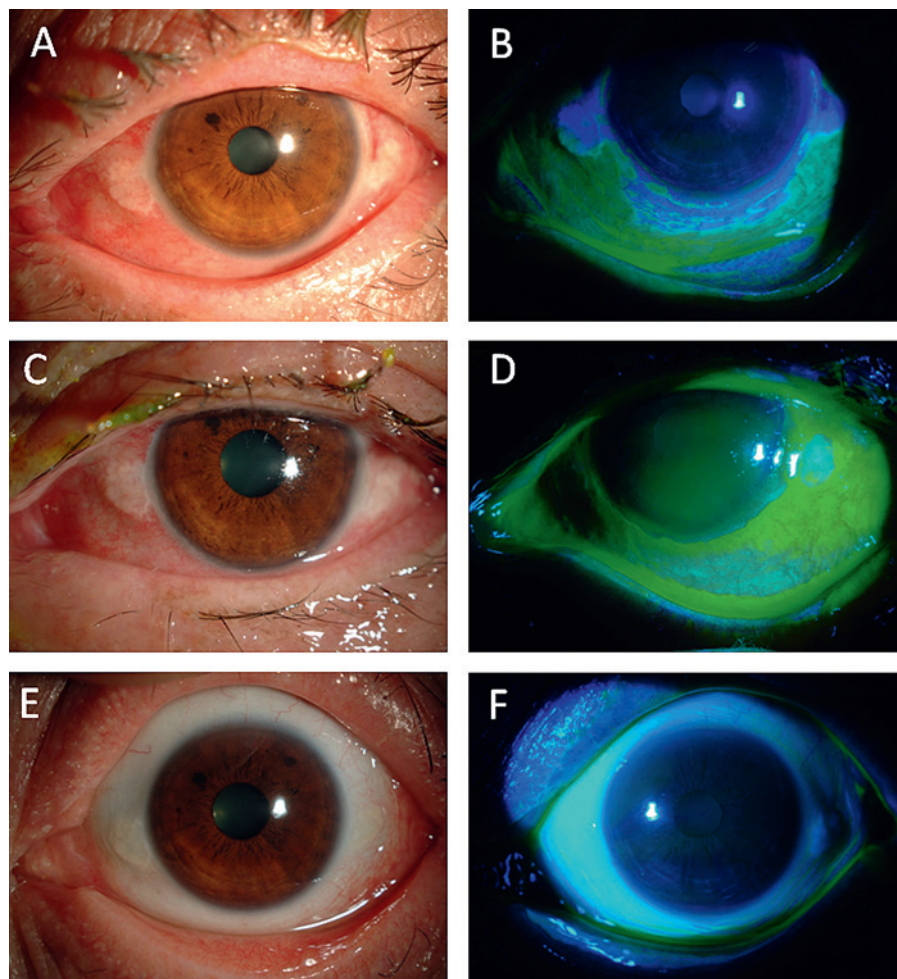


Figure 1 Appearances of the patient's left eye. Mild conjunctival hyperaemia (A) and large conjunctival epithelial defect (B) were seen on day 1 (the day that systemic eruption began). Depletion of the cilia occurred at day 3 (C) and the conjunctival epithelial defect enlarged (D). After steroid pulse therapy and intensive topical betamethasone, the conjunctival epithelium healed completely by day 23 (E, F).

using a well-documented SJS case supports the interesting hypothesis that the ophthalmological manifestations of SJS/TEN, in association with the systemic features of the disease, are strongly correlated with a severe cytokine storm arising on the ocular surface.

Various treatments have been proposed to manage SJS/TEN during the acute phase of the disease, including steroid pulse therapy, plasmapheresis, intravenous immunoglobulin, cyclophosphamide therapy and amniotic membrane transplantation.^{1 5} However, the choice of treatment regimens has been empirical, rather than based on the immunological mechanisms underlying the disease. Now, it is reasonable to speculate that a steroid pulse therapy is effective in controlling a cytokine storm. After steroid pulse therapy, our patient's general condition, including her skin rash, had markedly improved, and serum cytokine levels decreased coordinately. Bilateral conjunctival erosion extended to nearly the entire bulbar conjunctiva by day 3 (figure 1C,D). Thereafter, her conjunctival

epithelium began to regenerate and healed completely by day 23 with decrease in tear cytokines to the baseline levels (figure 1E,F). Her visual acuity 2 years after disease onset was 20/20 in both eyes and no cicatricial changes exist. This clinical outcome correlates with our previous report describing the therapeutic importance of a corticosteroid pulse and topical betamethasone at disease onset for reducing the degree of ocular complications.^{2 6} In conclusion, it is highly possible that an ocular cytokine storm and its suppression by therapeutic modalities such as those using steroids greatly influence the visual prognosis in SJS/TEN.

Acknowledgements The authors wish to thank John Bush for reviewing this manuscript.

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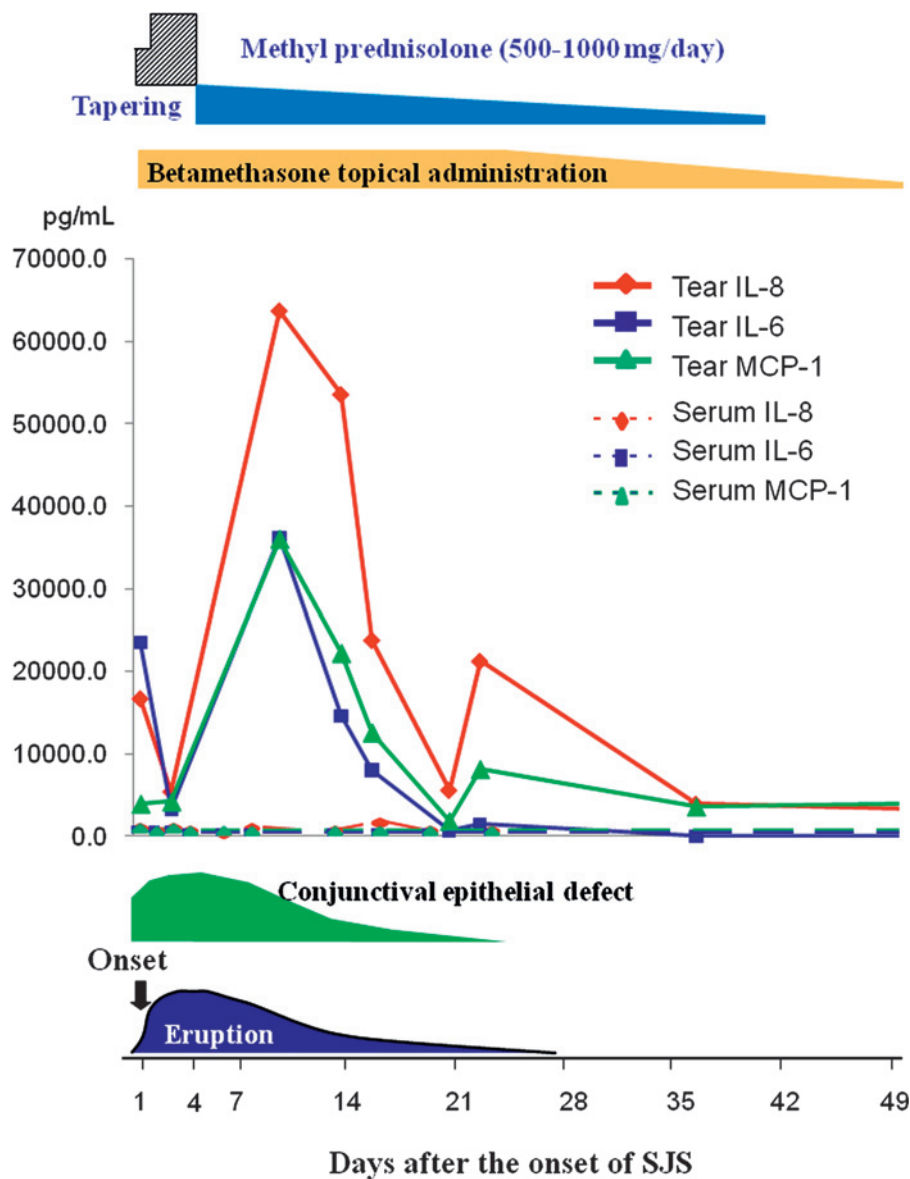


Figure 2 The interleukin (IL)-6, IL-8 and monocyte chemoattractant protein-1 (MCP-1) levels in the patient's tears and serum. SJS, Stevens-Johnson syndrome.

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Funding Health and Labor Sciences Research Grants (Research on Intractable Diseases) from the Ministry of Health, Labour and Welfare of Japan, and the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Competing interests None.

Patient consent This study was performed in accordance with the tenets set forth in the Declaration of Helsinki and written informed consent was obtained from the patient prior to involvement in the study.

Ethics approval Ethics approval was provided by the Institute Review Board (IRB) of Kyoto Prefectural University of Medicine, Kyoto, Japan.

Provenance and peer review Not commissioned; externally peer reviewed.

Accepted 20 March 2011

Br J Ophthalmol 2011; ■:1–2.
doi:10.1136/bjo.2010.196295

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Br J Ophthalmol published online April 11, 2011

doi: 10.1136/bjo.2010.196295

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Published online April 11, 2011 in advance of the print journal.

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