Successful Treatment of Toxic Epidermal Necrolysis/Stevens-Johnson Syndrome Overlap with Human Granulocyte Colony Stimulating Factor: A Case Report

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The strategy for the specific treatment of toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (SJS/TEN overlap syndrome) is controversial (1, 2). Immediate withdrawal of possible triggering drugs is mandatory. Supportive treatment in an intensive care unit (ICU) is optimal for detecting and treating complications. The rarity of the disease impedes performance of controlled treatment studies, and case reports constitute an alternative source of information, providing some evidence for choice of treatment. We report here the case of a 15-year-old boy with SJS/TEN overlap who was treated successfully with granulocyte colony stimulating factor (G-CSF) (filgrastim, Neupogen®, Amgen Europe BV, The Netherlands).

CASE REPORT

A 15-year-old boy presented with a 4-day history of flu-like symptoms, high fever, general malaise and headache. Initially, the headache was treated with one dose of a combination of acetysalicylic acid (500 mg) and codeine (10 mg), and after 3 days he developed a maculopapular rash, which appeared first on the trunk and progressed to the extremities and face. He was admitted to hospital and initially treated with an intravenous antibiotic (cefuroxime) on suspicion that infection was the triggering agent. The day after admission physical examination revealed an ill patient with a symmetrically distributed spotty, dusky-coloured, erythematous exanthema on the upper trunk and upper thighs. Flaccid bullae were noted and Nikolsky’s sign was positive. Bullae on the affected area were easily extended sideways by light pressure (indirect Nikolsky’s sign). New disseminated flaccid blisters filled with serous liquid appeared during the physical examination. There were severe mucosal erosions in the oral cavity, but no involvement of the conjunctiva and genital mucosa.

A clinical diagnosis of SJS/TEN overlap was made, and was confirmed with a skin biopsy for frozen and routine histology.

Microscopy of detached skin displayed total necrosis of the epidermis, covered by a normal basket weave stratum corneum. A 4-mm punch biopsy from the trunk just outside the detachment area showed confluent, almost full-thickness epidermal necrosis, with numerous apoptotic keratinocytes among the remaining basal cells. A sparse lymphocytic infiltrate was seen in the dermoepidermal interphase.

Laboratory investigations on admission included: white blood cell count 1.4 10⁹/l; platelet count 66×10⁹/l; C-reactive protein (CRP) 15 mg/l; albumin 30 g/l. Blood cultures and serological tests for Herpes simplex virus, Cytomegalovirus, and Epstein Barr virus were negative. Chest X-ray and echocardiogram results were within normal limits.

Leukocytes decreased to 0.9 10⁹/l the next day and the patient was transferred to the ICU. The calculated SCORTEN (SCORe of Toxic Epidermal Necrosis) score was 1, and the hospital mortality rate was estimated as 3.2% (3).

The patient was also classified using standard severity of illness scoring systems after admission to the ICU, and found to have an Acute Physiology and Chronic Health Evaluation (APACHE II) score of 20 (a score between 0 and 71, where a higher score implies severe disease and higher risk of death) as well as a Simplified Acute Physiology Score (SAPS II) of 32 (which provides an estimate of the risk of death without knowing the diagnosis) (4, 5). During the patient’s stay in the ICU he developed dyspnoea (chest X-ray showed bilateral pulmonary infiltrates) necessitating non-invasive ventilation. The patient was also polyuric and hypotensive and required large quantities of intravenous fluids as well as infusion of noradrenaline.

The detached skin was left in place and a neutral cream was applied to the eroded areas, which were covered with non-adherent bandage material.

Intensive care management was provided in a temperature-controlled environment (32ºC) and the only specific drug initiated immediately to supplement antibiotics was filgrastim, given over a 3-day period at a daily dose of 5 µg/kg subcutaneously.

The patient was treated in an aseptic manner and nursed on an air mattress. Parenteral nutrition was given. Epidermal detachment progressed to 25% of the skin surface, and dusky red macular erythema affected 70–80% of the body surface area. Progression ceased within 1 day after starting treatment with filgrastim. The antibiotic was discontinued one day after treatment with G-CSF was initiated. The time between the start of development of skin lesions and the maximum level of skin detachment was 4 days.

The patient was discharged from the ICU at day 7 after admission, with almost complete skin re-epithelialization, and discharged without complications after 13 days.
DISCUSSION

The cause of the patient’s SJS/TEN overlap is unknown. The single dose of a combination of acetylsalicylic acid and codeine was considered to be an aetiological factor, but both drugs also have a high risk for confounding by indication, since they are used either to treat the first symptoms of the disease itself, or an infection which may be the cause of the disease (6, 7).

TEN and SJS/TEN overlap are rare, acute and potentially fatal diseases, which are most commonly drug-induced. There is no specific treatment, except for standard supportive care in the ICU. Active treatment with cyclosporin or intravenous immunoglobulin was considered initially, but we were surprised by the rapid improvement within 24 h of the introduction of filgrastim, and decided to withhold supplementary treatment.

Neutropaenia is correlated with a poor prognosis in TEN (8). Therefore, the patient was treated with G-CSF, which appears to accelerate the re-epithelialization. The mechanism is not known. Delayed re-epithelialization has been observed in GM-CSF “knock-out mice” compared with wild types (9).

Endogenous G-CSF is produced by monocytes, fibroblasts and endothelial cells. In the bone marrow, it regulates the production of neutrophils (10) and induces immunotolerance by activating CD4+ CD 25+ regulatory T-cells (Tregs) from the bone marrow. This seems to prevent further tissue damage and facilitate faster recovery (9).

In the case described here the white blood cell count recovered to a normal level the day after starting treatment with filgrastim, and re-epithelialization was completed after 7 days. The fast recovery seen in this patient was striking and may encourage a controlled open trial based on a clear protocol, as has been done for cyclosporin and intravenous immunoglobulin in the treatment of TEN (11, 12).

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REFERENCES