Carbamazepine Induced Steven Johnson Syndrome/Toxic Epidermal Necrolysis Overlap Treated Successfully with Oral Cyclosporin

Case report and literature review

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Abstract
Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life threatening mucocutaneous drug reactions. Several therapies have been used in the treatment of SJS/TEN but none of them have been established as the gold standard treatment, until now. Studies showed that cyclosporine (CsA) can be used off-label in TEN/SJS and has shown promising therapeutic effectiveness in such diseases. Here we report a 38 year-old woman who presented to Ar Rustaq Hospital, Rustaq, Oman in 2019 with SJS/TEN overlap and was treated successfully with CsA along with supportive management. This case report also includes a literature review on use of CsA in the treatment of SJS/TEN.

Keywords: Steven Johnson Syndrome; Toxic epidermal necrolysis; Epidermal necrolysis; cyclosporine; Drug eruption; case report; Oman

Introduction
Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are skin conditions seen following reactions to certain drugs.1-4 Several therapies can be used to treat SJS/TEN, however, there is currently no standard treatment option.5 Previous studies have shown that cyclosporine (CsA) can be used to treat SJS/TEN, off-label, and has shown promising therapeutic effectiveness in curing similar diseases, despite the fact that its therapeutic role is
still not well understood. Here we present a case of SJS/TEN in Oman successfully treated using oral CsA, along with supportive management, and a literature review of the use of CsA in the treatment of SJS/TEN.

**Case Report**

A 38-year-old Indian female nurse was admitted to Ar Rustaq Hospital, Rustaq, Oman in 2019 with a 3 day history of fever and sore throat, as well as skin eruptions and oral mucosal and conjunctival ulcerations. She did not suffer from any chronic diseases apart from recurrent arthralgia and was not on any regular medications, except for various pain killers for her arthralgia, as needed. Additionally, she did not have any drug allergies. Her symptoms started on day 10 of her using carbamazepine. She had been taking carbamazepine for the first time as a pain killer after several failed pain medications. The patient was admitted for one day to a private healthcare facility where she was prescribed with intravenous (IV) hydrocortisone, IV antibiotics and her intake of carbamazepine was stopped. Unfortunately, her condition deteriorated, and she developed dysphagia. She decided to leave against medical advice to seek a second medical opinion. Consequently, she was admitted to Ar Rustaq Hospital after 3 days of her symptoms.

The initial examination of the patient revealed her to be very ill and dehydrated, febrile and tachycardiac. Her skin examination showed multiple maculopapular rash covering over 50% of body surface area (BSA) (using the rule of nine), with some dusky areas. There was skin peeling over the ear pinna, cheeks and abdomen (around 15% of her BSA) with some flaccid bullae over the anterior aspect of the neck and acral areas [Figure 1]. The blistered area was positive for Nikolsky’s sign. Red conjunctival mucosa with multiple erosions in the mouth and genital mucosa were noted as well.

Initial laboratory results revealed elevated C-reactive protein levels (139 mmol/L), elevated erythrocyte sedimentation rate (49 mm/h), a normal white blood cell count of 4.7 10³/µL with normal differential counts (neutrophils 2.89 10³/µL and eosinophil 0.05 10³/µL), normal random blood sugar levels and normal renal (including electrolytes, creatinine and urea) and liver function tests.
A multidisciplinary team was involved in patient management, including ophthalmology, dentistry, ear, nose and throat (ENT), internal medicine and dermatology. She was initially admitted to the intensive care unit for monitoring and was then moved to the medical ward.

She was managed with IV hydration, frequent petroleum jelly application on the skin lesions and heparin prophylaxis. She was started on an oral dose CsA of 5 mg/kg/day. At Ar Rustaq Hospital, CsA is considered to be cost-effective and readily available compared to other alternative therapies, such as IV immunoglobulin (IVIg), Etanercept and plasmapheresis. The patient gradually improved and showed skin re-epithelization on day 3 of CsA administration. Additionally, no new skin lesions were noted. She was then discharged on day 6, when her dose was reduced to 3 mg/kg/day.

The patient came in for a follow-up appointment in the dermatology clinic after 9 days and was showing remarkable improvement. Subsequently, the CsA was stopped. In total, she had received a gradually decreasing dose of CsA for 15 days [Figure 2]. The patient has given informed consent for the publication of her case in a medical journal.

Discussion

SJS and TEN are severe mucocutaneous drug reactions. The difference between these two conditions is based on the percentage of BSA involvement and type of skin lesions. SJS involves around 10% of BSA, plus widespread erythematous, purpuric macules or flat atypical target lesions. An overlap of the two conditions, SJS/TEN, involves between 10% and 30% of BSA, plus widespread erythematous, purpuric macules or atypical target-like annular patches. TEN, alone, is indicated by 30% of BSA involvement, plus widespread erythematous, purpuric macules or atypical target lesions. TEN without spots leads to large epidermal sheets, of around 10% BSA, without purpuric macules or target lesions.\textsuperscript{1,3} The overall combined incidence of SJS, SJS/TEN overlap, and TEN is estimated to be 2-7% per million cases per year, with a mortality rate of approximately 25%-35%.\textsuperscript{1,2} SJS/TEN can manifest through varying symptoms, such as high-grade fever, mucositis, anxiety, painful swallowing and skin pain/burning. These symptoms are then followed by cutaneous lesions, like target lesions, vesicles and bullae, and rapidly progressing sloughing of the skin within a few days.\textsuperscript{1} The case detailed here fits the category of SJS/TEN overlap, given that she had peeling and blistering of around 10-15% of BSA and widespread maculopapular skin lesions.
The pathogenesis of SJS/TEN is still not well understood. Most of the cases are preceded by exposure to certain medications. Many medications have been identified as the likely cause of SJS/TEN, such as NSAIDs, anti-convulsants, antibiotics and allopurinol. Other non-drug causes of SJS/TEN are mycoplasma pneumonia infection, HIV, dengue virus, the mumps-rubella vaccination and the use of contrast for imaging. Certain genetic factors have also been found to be associated with an increased risk of SJS/TEN. The patient in this case was of Indian origin who developed SJS/TEN after taking carbamazepine. Being of Indian or Asian origin increases the risk of anticonvulsant-induced SJS/TEN, as individuals of this nationality have a high prevalence of the HLA-B*1502 phenotype. Unfortunately, we did not send for the HLA phenotyping for this patient, due to technical and financial reasons.

Management of SJS/TEN should be initiated by first discontinuing the suspected agent, along with comprehensive supportive care. A multidisciplinary team should be created to involve critical care experts, including dermatology, infectious disease, ophthalmology, ENT surgeons, wound care nurse and a dietician. Supportive care is best delivered in the burn or intensive care unit, which would mainly focus on the assessment of airway, renal function, fluid and electrolyte balance, nutrition, skin and ocular surfaces, pain control and prevention of infection.

In addition to supportive care, several potential therapies have been proposed, including IVIg, glucocorticoids, plasmapheresis, CsA and TNF-a inhibitors (such as etanercept). However, none of these therapies have been established as the gold standard treatment of SJS/TEN, until now. CsA is a well-established medication which has been used to cure several dermatological diseases. A review of the current literature indicates that CsA may slow down the progression of SJS/TEN. CsA has been found to be effective in reducing the mortality rate of SJS/TEN, the duration of recovery and contributing to early discharge from the hospital.

The proposed mechanism of action of CsA in SJS/TEN is through inhibiting the T cell function, reducing production of cytokines by cytotoxic T cells and natural killers cells. Additionally, it reduces granulysin levels, which has recently been noted to have an important role in the pathogenesis of SJS/TEN related to cell apoptosis.
An observational record-based study compared the use of CsA and supportive treatment to using supportive treatment alone. It was found that the standardized mortality ratio was 0.32 in CsA group, which is nearly 3.3 times lower than the supportive treatment group. Moreover, the time of re-epithelization of the skin, duration of recovery and stabilization were significantly lower in CsA group, at $P = 0.007$, $P = 0.01$ and $P < 0.001$, respectively.\(^7\)

A meta-analysis by Gonzalez et al. assessed 71 patients with epidermal necrolysis (EN), of which 49 patients were treated with CsA, and of these 5 patients died (10.2%). It should be noted that in this group, 11.8 (24.1%) deaths were expected, according to the Score for Toxic Epidermal Necrolysis. Of the 22 patients who were treated with non-CsA therapies, 7 died (31.8%), with 6.4 deaths (29.1%) expected.\(^8\)

In 2018, a meta-analysis of 9 observational studies, with a total of 256 SJS/TEN patients, revealed a significant reduction in risk of mortality following CsA therapy (standardized mortality ratio of 0.320; 95% CI: 0.119–0.522; $P = 0.002$).\(^2\) In addition, a retrospective study from 2014 revealed that the use of CsA over IVIg may offer a greater chance of recovery in the SJS/TEN treatment (standardized mortality ratio of 0.43 over 1.43, respectively).\(^9\) In 2010, Allanore et al. conducted the first open phase II trial to determine the safety and possible benefit of cyclosporin treatment for SJS and TEN. That study concluded that CsA lowered both the death rate and the progression of detachment greater than expected.\(^10\)

The results of these studies support the effectiveness of CsA (at a dose of 3-5 mg/kg per day as early as possible) in reducing the chance of mortality and rapid cessation of the SJS/TEN disease progression.\(^2\;3\;6\;10\)

**Conclusion**

This case report demonstrates a successful experience of using CsA, along with supportive care, in the management of SJS/TEN overlap. This finding was supported following a thorough review of the currently available literature. However, future randomized controlled trials would be the most effective in confirming the efficacy of CsA.

**References**


Figure 1: Maculopapular rash with some dusky areas and skin peeling, seen at admission.

Figure 2: The patient 2 months after first presentation.