Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute life-threatening mucocutaneous drug reactions. Several therapies have been used to treat SJS/TEN; however, there is currently no standard treatment option. Previous studies have shown that cyclosporine (CsA) can be used to treat SJS/TEN off-label. CsA has shown promising therapeutic effectiveness in curing similar diseases, although its therapeutic role has not yet been fully understood.

Here, we present a case from Oman of SJS/TEN being successfully treated using oral CsA and providing supportive management. The current report will also provide a brief review of the literature concerning the use of CsA in the treatment of SJS/TEN.

Case Report

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

The initial examination of the patient revealed her to be very ill, dehydrated, febrile and tachycardiac. Her skin examination revealed multiple maculopapular rashes covering over 50% of body surface area (BSA; using the rule of nines), 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 part 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 also noted.

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 x 10^3/µL with normal differential counts (neutrophils 2.89 x 10^3/µl and eosinophil 0.05 x 10^3/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 those drawn from the fields of ophthalmology, dentistry, ear, nose and throat (ENT), internal medicine and dermatology. The patient had...
initially been admitted to the intensive care unit for monitoring purposes and was then shifted to the medical ward. She was managed with IV hydration, frequent petroleum jelly application on the skin lesions and heparin prophylaxis. Furthermore, she was started on an oral dose of 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-epithelisation on day three of CsA administration. Additionally, no new skin lesions were noted. She was then discharged on day six when her dose was reduced to 3 mg/kg/day.

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 detachment 10% of BSA, plus widespread erythematous, purpuric macules or flat atypical target lesions. An overlap of the two conditions, SJS/TEN, involves detachment 10–30% of BSA, plus widespread erythematous, purpuric macules or atypical target-like annular patches. TEN, alone, is detachment of 30% of BSA, 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. 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%. SJS/TEN can manifest through varying symptoms such as fever, mucositis, anorexia, and skin tenderness. These symptoms are then followed by cutaneous lesions, such as targetoid lesions, vesicles and bullae in addition to rapidly progressing sloughing of the skin within a few days. The case detailed here fits the category of SJS/TEN overlap, given that the patient had peeling and blistering of around 10–15% of BSA and widespread maculopapular skin lesions.

The pathogenesis of SJS/TEN has not yet been sufficiently 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, anticonvulsants, antibiotics and allopurinol. Other non-drug causes of SJS/
TEN include mycoplasma pneumonia infection, HIV, dengue virus, the mumps-rubella vaccination and the use of contrast agents for imaging purposes. 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 and developed SJS/TEN after taking carbamazepine. Being of Indian or Asian origin increases the risk of anticonvulsant-induced SJS/TEN, as individuals of these nationalities have a high prevalence of the HLA-B*1502 phenotype. Unfortunately, the HLA phenotyping for this patient could not be sent for due to technical and financial reasons.

Management of SJS/TEN should be initiated by first discontinuing the suspected agent, along with providing comprehensive supportive care. A multidisciplinary team should be created involving critical care experts, including those belonging to dermatology, infectious disease, ophthalmology and ENT fields along with a 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 yet been established as the gold standard treatment for SJS/TEN. CsA is a well-established medication that has been used to cure a number of 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 function, reducing the production of cytokines by cytotoxic T cells and natural killer 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 with using supportive treatment alone. It was found that the standardised mortality ratio was 0.32 in the CsA group, which is nearly 3.3 times lower than that in the supportive treatment group. Moreover, the time of re-epithelisation of the skin, duration of recovery and stabilisation were significantly lower in the CsA group, at P = 0.007, P = 0.01 and P < 0.001, respectively. A meta-analysis by Gonzalez et al. assessed 71 patients with epidermal necrolysis. Of these, 49 patients were treated with CsA and five of the treated patients died (10.2%). It should be noted that in this group, 11.8 (24.1%) deaths were expected, according to the score for TEN. Of the 22 patients who were treated without CsA therapies, seven died (31.8%), when 6.4 deaths (29.1%) were expected.

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

The results of these studies support the effectiveness of CsA (at a dose of 3–5 mg/kg/day, starting treatment at the earliest) in reducing the chance of mortality and rapid cessation of the SJS/TEN disease progression.

Conclusion

This case report demonstrates a successful experience of the administration of 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 randomised controlled trials would be the most effective in confirming the efficacy of CsA.

Authors’ Contribution

All authors were involved in the treatment of the patient. RA collected all the patient’s data and took her consent. RA and TA conducted the literature review, drafting and revising of the manuscript. All authors read and approved the final version of the manuscript.

References

1. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I: Introduction, history, classification, clinical features, systemic manifestations, etiology and immunopathogenesis. J Am Acad Dermatol 2013; 69:173.e1–13. https://doi.org/10.1016/j.jaad.2013.05.003.

2. Ng QX, Deyn MLZQD, Venkatanarayanan N, Ho CYX, Yeo WS. A meta-analysis of cyclosporin treatment for Stevens-Johnson Syndrome/Toxic epidermal necrolysis. J Inflamm Res 2018; 11:135–42. https://doi.org/10.2147/JIR.S160964.
3. Thong B. Stevens-Johnson syndrome / toxic epidermal necrolysis: an Asia-Pacific perspective. Asia Pac Allergy 2013; 3:215–23. https://doi.org/10.5415/apallergy.2013.3.4.215.

4. Stern RS, Divito SJ. Stevens-Johnson syndrome and toxic epidermal necrolysis: Associations, Outcomes and Pathobiology: Thirty Years of progress but Still Much to be Done. J Invest Dermatol 2017; 137:1004–8. https://doi.org/10.1016/j.jid.2017.01.003.

5. Schneider JA, Cohen PR. Stevens-Johnson syndrome and toxic epidermal necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures. Adv Ther 2017; 34:1235–44. https://doi.org/10.1007/s12325-017-0530-y.

6. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II: Prognosis, sequel, diagnosis, differential diagnosis, prevention and treatment. J Am Acad Dermatol 2013; 69:187e1–16. https://doi.org/10.1016/j.jaad.2013.05.002.

7. Mohanty S, Das A, Ghosh A, Gharami RC, Bandypadhyay D, et al. Effectiveness, safety and tolerability of cyclosporine versus supportive treatment in Stevens–Johnson syndrome/toxic epidermal necrolysis: A record-based study. Indian J Dermatol Venereol Leprol 2017; 83:312–16. https://doi.org/10.4103/ijdvl.IJDVL_201_16.

8. Gonzalez-Harrada C, Rodriguez-Martín S, Cochaferio I, Lerma V, Gonzalez O, Lorente JA, et al. Cyclosporin Use in Epidermal Necrolysis in Associated with an Important Mortality Reduction: Evidence from Three Different Approaches. J Invest Dermatol 2017; 137:2092–100. https://doi.org/10.1016/j.jid.2017.05.022.

9. Kirchhof MG, Milewczewski MA, Sikora S, Papp A, Dutz JP. Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporin. J Am Acad Dermatol 2014; 71:941–7. https://doi.org/10.1016/j.jaad.2014.07.016.

10. Valelyie-Allanore L, Wolkenstein P, Brochard L, Ottonen N, Maître B, Revus J, et al. Open trial of cyclosporin treatment for Steven-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 2010; 163:847–53. https://doi.org/10.1111/j.1365-2133.2010.09863.x.