Case report

Stevens-Johnson syndrome/toxic epidermal necrolysis: treatment with low-dose corticosteroids, vitamin C and thiamine

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SUMMARY

We present the case of a 33-year-old woman with no significant past medical history who was admitted to an outside hospital for the abrupt onset of fevers, malaise and a diffuse mucocutaneous rash. Her constellation of symptoms and presentation were most consistent with a diagnosis of Stevens-Johnson syndrome/toxic epidermal necrolysis overlap syndrome secondary to ibuprofen exposure. Her rash continued to worsen and she was transferred to our medical intensive care unit (ICU), where broad-spectrum antibiotics were discontinued and she was treated with supportive care as well as 'low-dose' intravenous hydrocortisone, ascorbic acid (vitamin C) and thiamine (HAT therapy). After starting this therapy, the patient demonstrated a dramatic response with rapid improvement of her cutaneous and mucosal lesions. She was tolerating a diet provided by the hospital on day 4 and was discharged from the ICU a few days later.

BACKGROUND

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap syndrome encompass a spectrum of diseases characterised by a T-cell-mediated drug reaction which induces keratinocyte apoptosis.¹ Clinically, patients present with a prodrome of flu-like symptoms, severe mucocutaneous reactions and extensive necrosis and detachment of the epidermis. Lesions progress to vesicles and bullae, and within days the skin begins to slough.² SJS/TEN are life-threatening diseases with an overall mortality of about 22%.³ Currently, treatment consists largely of withdrawal of any offending agents and supportive care. Immunomodulating therapies have been investigated and glucocorticoids may provide a survival benefit; however, more definitive research is needed.

CASE PRESENTATION

A 33-year-old Moroccan woman immigrant with no significant past medical history presented to an outside hospital complaining of a 3-day history of dry cough, shortness of breath, chest pain, fevers and sore throat. Shortly thereafter, she noted a diffuse rash involving her trunk, extremities, oral mucosa and genitalia. Her symptoms and rash occurred prior to admission to the outside hospital. She reported taking 'many' ibuprofen tablets at the

onset of symptoms without relief. She denied taking any other medications including over-the-counter medications and complementary/alternative therapies. She did not volunteer any accompanying urinary, gastrointestinal or neurologic complaints. She did not report any recent travel history or sick contacts. She was on no regular medications and her only reported allergies were to chocolate and milk containing products, which caused a mild, pruritic rash in the past. She denied any illicit drug abuse, is a non-smoker and seldom drinks alcohol. On presentation, she had a fever of 39.2°C and was tachycardic with otherwise normal vital signs. She was admitted to an outside hospital with the diagnosis of 'acute viral syndrome of unknown aetiology'. While on the medical ward, she remained febrile and examination revealed severe conjunctival injection, haemorrhagic crusting of the lips with oral ulcerations and petechiae in the posterior pharynx without exudate or swelling. Her neck was supple without masses or lymphadenopathy and she had a benign cardiopulmonary and abdominal examination. Skin examination revealed diffuse crusted erosions with areas of confluence most concentrated from the waist up (figure 1). Her genitourinary exam revealed maculopapular and ulcerative lesions in the groin/perineum with partial fusion of the labia and exquisite tenderness to palpation. Given the severity and distribution of her rash, there was concern for SJS/TEN and she was transferred to the medical intensive care unit (MICU) of our hospital (a tertiary care teaching hospital), 5 days after initial presentation. She developed sloughing of the skin, pustules with severe oral, ocular and vaginal involvement. On arrival at our hospital, dermatology, ophthalmology, otolaryngology and gynaecology were consulted.

INVESTIGATIONS

A complete blood count was only significant for thrombocytopenia (120 000/μL). A comprehensive metabolic panel and urinalysis were normal. Chest radiograph was normal. Her beta-human chorionic gonadotropin, troponins, influenza A/B, mononucleosis, mycoplasma and streptococcal pharyngitis screening tests were negative. Her blood cultures showed no growth and cerebrospinal fluid analysis was unremarkable. A skin biopsy of lesional skin,

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Figure 1 Initial presentation to our MICU depicting diffuse maculopapular rash with facial (A), chest (B) and abdominal (C) involvement. MICU, medical intensive care unit.

adjacent to a blister, demonstrated necrosis of the epidermis with minimal perivascular infiltrate within the dermis.

DIFFERENTIAL DIAGNOSIS

The patient was diagnosed with SJS/TEN overlap syndrome likely secondary to ibuprofen. It was possible that the use of other undisclosed medication may have triggered the SJS/TEN. Other initial considerations included drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme major, exanthematous drug eruptions, viral exanthem, generalised bullous fixed drug eruption and bullous pemphigoid. She did not have a peripheral eosinophilia to suggest DRESS. In erythema multiforme major, the skin lesions consist of typical targets or raised atypical targets and are predominantly localised on the extremities. Patients with generalised bullous fixed drug eruption and exanthematous drug eruptions typically lack mucosal involvement and the prominent skin pain of SJS/TEN. The classical clinical findings in bullous pemphigoid are tense, fluid-filled bullae on skin. Her prodromal symptoms, skin and mucous membrane findings following ibuprofen exposure, the disease course, the histopathological features on skin biopsy and the laboratory findings were most consistent with SJS/TEN overlap.

TREATMENT

On arrival to the MICU, the patient was being treated with parenteral antibiotics including cefepime, doxycycline, metronidazole and vancomycin. These antibiotics were started at the outside hospital after presentation of her symptoms and rash. A urinary catheter was placed. Treatment with intravenous hydrocortisone 50mg every 6 hours, intravenous ascorbic acid 1500mg every 6 hours and intravenous thiamine 200mg every 12 hours was initiated (HAT therapy). She was also receiving erythromycin, moxifloxacin and prednisolone eye drops. Systemic antibiotics were stopped on hospital day 2 as all cultures were negative. Skin care included mupirocin and triamcinolone ointment, vaseline and xeroform gauze.

OUTCOME AND FOLLOW-UP

A dramatic improvement was noted within 48 hours of initiating HAT therapy with daily improvement of skin lesions thereafter (figure 2). She remained haemodynamically stable and was afebrile beginning hospital day 2. By day 4 she was tolerating soft foods and by day 7 her mucosal lesions had significantly improved. Her labia were no longer fused and no vaginal or cervical involvement was observed on speculum examination. On day 8, amniotic membrane transplants were placed by ophthalmology for ongoing bilateral palpebral and bulbar

Figure 2 Progressive improvement of rash over hospitalisation course.

Figure 3 Depiction of rash on day of discharge.

conjunctiva inflammatory changes. She was transferred to the general medicine ward on day 9, at which time HAT therapy was discontinued. She was discharged from the hospital on day 11 (figure 3) with ophthalmology follow-up.

DISCUSSION

SJS/TEN are severe cutaneous adverse reactions characterised by varying degrees of epidermal detachment and erosion of the mucous membranes. Medications are the most commonly reported causes of SJS/TEN, with sulphonamides, carbamazepine, non-steroidal anti-inflammatory drugs, allopurinol, phenytoin and phenobarbital being the most common culprit agents.⁴ SJS/TEN typically occurs 4–21 days after starting use of the offending drug. Less commonly SJS/TEN are caused by *Mycoplasma pneumoniae*, herpes simplex virus and cytomegalovirus infections. SJS/TEN is more common in women than in men with evidence of a genetic predisposition in certain ethnic groups. Patients with HIV infection and malignancy are at an increased risk of developing SJS/TEN.⁴

Cutaneous lesions typically first appear on the thorax and face before spreading to other areas in a symmetrical distribution.⁴ Mucosal involvement occurs in almost all cases, most commonly presenting as stomatitis and conjunctivitis. Systemic features are not uncommon and include septicemia, acute kidney failure, pneumonia, acute lung injury and hepatitis. Sepsis is the most common cause of death in these patients. The mortality of SJS/TEN is approximately 22% with survivors developing significant long term sequelae.⁵ While the clinical presentation may be highly suggestive of SJS/TEN, histopathology of a skin biopsy is required to confirm the diagnosis and exclude other blistering dermatoses.⁵

Currently, there is a paucity of evidence to support a standardised treatment protocol for this rare spectrum of diseases. Most approaches focus on withdrawal of any offending agent and supportive care. The 2016 UK guideline for the management of SJS/TEN is considered the reference standard.⁵ As patient drug histories are notoriously unreliable every effort must be made to identify all possible triggering drugs. It is crucial to withdraw the triggering drug and ensure no further exposure to the implicated drug and related agents. Identification of the causative drug may be reasonably simple in cases where a single drug is implicated but may be difficult when the patient has been exposed to multiple drugs. The main principles of supportive care are the same as for major burns and include wound care, fluid and electrolyte management, nutritional support,

temperature management, pain control and monitoring or treatment of superinfections. Patients are therefore best managed in a specialised ICU for critical care management and specialist nursing care.⁵ The optimal approach to wound care in SJS/TEN has not been determined, and different approaches are used at different centres. Bland emollients, such as petroleum gauze provide a barrier and moisturising layer to help reepithelisation. Topical antibiotics may be applied to sloughed area that have a high risk of superinfection.^{4,5}

The role of systemic immunomodulating agents is the management of SJS/TEN is controversial. A systematic review and meta-analysis by Zimmermann *et al* on 3248 patients compared the efficacy of standard supportive care versus systemic immunomodulatory therapies.⁶ Glucocorticoids provided a survival benefit in three analyses but were only statistically significant in one. The dose of glucocorticoid that has been evaluated in patients with SJS/TEN is much higher than the dose used in our patient. A short course of moderate-to-high dose systemic glucocorticoid (eg, prednisone 1–2 mg/kg/day for 3–5 days) has been described. In addition, high-dose intravenous pulses of methylprednisolone 500 or 1000 mg/day for 3–4 days, along with 0.1% betamethasone solution, 0.1% betamethasone eye ointment has been reported.⁷ Cyclosporine shows promise but current data is underpowered and may not be generalizable. Intravenous immunoglobulin therapy provided no mortality benefit when compared with supportive care. The use of thalidomide was associated with increased mortality and is not recommended.^{6,8}

In this case, we propose a novel treatment regimen based on the underlying pathogenic mechanism of SJS/TEN. Current research has suggested that drug-mediated SJS/TEN involves major histocompatibility class-I restricted activation of cytotoxic T lymphocytes and natural killer (NK) cells. Once activated, these cells secrete various cytotoxic signals including granulysin, perforin/granzyme B, Fas/Fas ligand, pro-inflammatory NF- κ B and various other cytokines/chemokines which mediate keratinocyte death and apoptosis.⁹ There is a substantial amount of scientific evidence to support the use of HAT Rx in the treatment of sepsis and other inflammatory states.^{10–12} Given the known inflammatory and pro-apoptotic mechanisms at play in SJS/TEN, we believe HAT therapy may be beneficial in the treatment of this rare spectrum of diseases. We present the scientific basis for our belief.

Stojadinovic *et al* studied the transcriptional profiles of human keratinocytes treated with and without dexamethasone.¹³ In addition to the known regulation of pro-inflammatory genes,

steroid treatment was found to suppress expression of interferon gamma regulated genes and receptors, repress pro-apoptotic genes and induce antiapoptotic genes in keratinocytes. Inhibition of pro-inflammatory NF- κ B (I κ B) was one of the earliest genes to be upregulated by glucocorticoid exposure.¹³ Glucocorticoid treatment has also been shown to reduce NK cell cytolytic activity by reducing messenger RNA expression for both perforin and granzyme B.¹⁴ Glucocorticoids alone have not convincingly been proven to be beneficial in the treatment of SJS/TEN; however, there appears to be a synergy between ascorbic acid and glucocorticoids in inflammatory states and oxidative conditions. Ascorbic acid has been shown to restore glucocorticoid receptor function and responsiveness in oxidative conditions.¹⁵ In turn, ascorbic acid mediated uptake via the sodium-vitamin C transporter is downregulated in inflammatory states and the administration of glucocorticoids has been shown to increase expression of this transporter.¹⁶ Huwiler *et al* demonstrated a dose dependent effect of ascorbic acid in reducing NK cell activity through scavenging and inactivating killing factors secreted by NK cells.¹⁷ Of particular interest in SJS/TEN is the multiple roles of ascorbic acid in skin health. Normal skin contains high amounts of ascorbic acid which has antioxidant, photoprotective, antiapoptotic effects and enhances barrier function.¹⁸ Duarte *et al* used microarray analysis to investigate the effect of ascorbic acid on human dermal fibroblasts, demonstrating increased mitogenic stimulation and fibroblast motility in wound healing and faster repair of oxidatively damaged DNA bases.¹⁹ Collectively, these findings support the role for ascorbic acid use in conjunction with glucocorticoids in the epidermal insult posed by SJS/TEN. Additionally, thiamine deficiency is common in critical illness and may compound mitochondrial injury and failure seen in vitamin C depleted states.²⁰

The disease course in SJS/TEN generally involves a period of worsening followed by either continued disease progression and death or slow improvement. With regard to our patient, she appeared to rapidly improve with HAT therapy. While a rapid resolution of the features of SJS/TEN has been previously described,⁵ the rapid improvement in our patient after starting HAT therapy was striking. We believe the synergistic effect of this metabolic resuscitation contributed to her improvement. Vitamin C alone and in combination with glucocorticoids and thiamine has been reported to be of benefit in patients with sepsis, acute respiratory distress syndrome and pancreatitis. Although patients with sepsis have been treated with HAT therapy, to date, side effects of this treatment protocol have not been reported.^{12 20} Currently, over 20 randomised controlled trials are registered at

the US National Library of Medicine ClinicalTrials.gov website; these studies will evaluate the benefit of HAT therapy in patients with sepsis.^{12 21 22} Review of these clinical trials is needed. This is the first report of the potential benefit of HAT therapy in patients with SJS/TEN. While we report on the potential benefit of HAT therapy in a single patient with SJS/TEN, this intervention, including the dose of steroids, requires substantial research as a potential treatment of this serious disease.

Contributors MMM participated in patient management, drafted the first version of the manuscript and reviewed the final version of manuscript. AZB participated in patient management, was responsible for taking and editing the pictures, edited the draft version of the manuscript and reviewed the final version of manuscript. AB participated in the care of the patient, helped in editing the pictures, edited the draft version of the manuscript, obtained consent from the patient and has reviewed the final version of manuscript. PEM was the consultant responsible for patient management, edited the draft version of the manuscript and reviewed the final version of manuscript. All authors approve the final version of the manuscript for publication.

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Learning points

- Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap syndrome are a spectrum of diseases characterised by a T-cell-mediated drug reaction which causes keratinocyte apoptosis.
- SJS, TEN and SJS/TEN overlap syndrome carry significant morbidity/mortality and there are currently no standardised treatment protocols for this rare spectrum of diseases.
- Current understanding of SJS/TEN disease pathogenesis supports the potential role for combination therapy with intravenous vitamin C, low-dose systemic corticosteroids and thiamine in the treatment of this disease. Further research and evaluation of intravenous hydrocortisone, ascorbic acid (vitamin C) and thiamine (HAT therapy) for SJS/TEN is needed.

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