Background

SJS and Toxic Epidermal Necrolysis (TEN) are among the most severe of a large spectrum of drug eruptions and are life-threatening reactions (1). They are as differing spectrums of the same disorder, with SJS involving less (2,3), TEN more (4).

• SJS is characterized by a prodrome of fever, rash, myalgia, or subcutaneous edema and appearance of erythematous macules, papules, or vesicles on the skin. The rash progresses to bullae and eventually skin sloughing. Disease progression culminates in epidermal death and sloughing of 10% or less of the body surface area (BSA), and involves at least two mucosal surfaces (ocular, oral, genital). TEN presents with a more severe subset involving skin and fever as high as 39°C, as well as cutaneous involvement of > 30% BSA.

• Drugs are the causative agent in at least 50% of SJS, and over 80% of TEN cases (5). The incidence of SJS/TEN is estimated at 2.8 cases/million/year with SJS occurring more commonly than TEN by approximately 3:1 (6-4).

• No laboratory tests will confirm a definitive diagnosis of SJS/TEN (7); Diagnosis is based solely on clinical history and examination. Early emergent presentation is critical,

• Basic principles of treatment are removal of the offending agent, and administration of supportive care (8,9). This is a critical time period, and even minor improvement in clinical condition can cause desquamation (8,9).

• Because of the rarity of SJS/TEN cases, retrospective case series act as the main source of data in this area. Currently, not enough cases exist to definitively establish general accepted standard of treatment (23).

Objective

• This case series evaluation aimed to determine the current local approach applied in the diagnosis and management of patients presenting with SJS/TEN, and to identify novel causative agents.

Methods

• Retrospective case series evaluation of electronic medical records of patient cases seen in the KGH emergency department and/or admitted to KGH from Jan 1, 2002 to Jan 1, 2010.

• ICD-9 codes (or equivalent based on year of patient visit codes), LS5 Bullous Erythema Multiforme, LS12 Toxic Epidermal Necrolysis and LS9 Unspecified Erythema Multiforme/PM.

• Details regarding patient sex, age, inciting agents, symptoms, management strategies, duration of illness, and outcomes were recorded for qualitative and descriptive analysis.

Table 1. Descriptive Values of Charts

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Prodrome</th>
<th>Drug</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77/f</td>
<td>27/f</td>
<td>Fever, weakness, “flu-like” symptoms</td>
<td>Carbamazepine/7d</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td>2</td>
<td>66/m</td>
<td>32/f</td>
<td>Maculopapular eruption beginning on the arm, spreading to</td>
<td>Clarithromycin/4d</td>
<td>TEN</td>
</tr>
<tr>
<td>3</td>
<td>75/m</td>
<td>51/f</td>
<td>Erythematous rash dorsum of feet, back of neck</td>
<td>Detrol/25d</td>
<td>SJS</td>
</tr>
<tr>
<td>4</td>
<td>72/f</td>
<td>82/f</td>
<td>Erythema multiforme, L512 Toxic Epidermal Necrolysis and L519 Unspecified</td>
<td>IVIG x 4 days, prednisone eye drops,</td>
<td>TEN</td>
</tr>
<tr>
<td>5</td>
<td>71/m</td>
<td>51/m</td>
<td>Pruritic erythema on legs, arms “clinically suggestive of SJS”</td>
<td>Valproic Acid/25d</td>
<td>SJS</td>
</tr>
</tbody>
</table>

Table 2. Summary of SJS Cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Prodrome</th>
<th>Eruption Description</th>
<th>Management/Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77/f</td>
<td>27/f</td>
<td>Fever, weakness, “flu-like” symptoms</td>
<td>Erythematous macules, papules and bulla, no desquamation</td>
<td>IVIG x 4 days, prednisone eye drops, oral prednisone 1%, gatifloxacin eye drops,</td>
</tr>
<tr>
<td>2</td>
<td>66/m</td>
<td>32/f</td>
<td>Fever, fatigue, weakness, nausea, vomiting, urinary urgency/frequency</td>
<td>Diffuse mucocutaneous necrosis, no ulceration, no target lesions, progressed to desquamation of skin on limbs, arms, legs</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>75/m</td>
<td>51/m</td>
<td>Fever, weakness, “flu-like” symptoms</td>
<td>Erythema multiforme macules on eyes, face, chin, no desquamation</td>
<td>IVIG x 3 days/survived/15</td>
</tr>
<tr>
<td>4</td>
<td>72/f</td>
<td>82/f</td>
<td>Maculopapular eruption beginning on the arm, spreading to</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Mean age of patients was 51.4 years (27 to 82); 35.7% were female. All cases but one were drug related. Mean time from initiation of the culprit agent to eruption of SJS was 15 days (range 1 to 34 days). Location of skin involvement was limited to less than 30% BSA in all cases, with the exception of one patient who had been taking allopurinol for 45 days, and one patient who was previously being treated for atop dermatitis with amoxicillin. All patients presented with clinical suspicion for a drug eruption, and all but one patient had a history of a prodrome. All cases involved six or more mucosal surfaces. Average hospital stay was 12 days. All cases but one were drug related. All but one patient survived. Hospital stay ranged from two days to 65 days, with all but two patients hospitalized for less than two weeks.

Discussion

• SJS/TEN are frequently misdiagnosed and underreported because lesions are often present for several days before being recognized, and the early clinical signs and symptoms can cause desquamation (8,9).

• There is an ongoing debate over whether all patients obtained their diagnosis on clinical grounds, although four had skin biopsies performed (cases 6, 8, 10, 11), three diagnosed as SJS (cases 7, 10, 11), and four patients were diagnosed as TEN (cases 1, 2, 3, 4). No evidence of the presence of acniform features, skin mottling, or desquamation was allowed in the diagnosis of TEN.

• The diagnosis is based on a quick clinical diagnosis and administration of treatment, the later stages of cutaneous progression may have been missed. There were only five of our fourteen cases for which cutaneous biopsy was attempted, but 6 of our 14 cases were diagnosed with TEN at the time of presentation.

• Literature review indicates that the most commonly implicated medications include antibiotics, acetaminophen, and anti-inflammatories, with anti-inflammatories (namely carbamazepine, lamotrigine, diltiazem, and phenobarbital) and non-steroidal anti-inflammatory drugs (NSAIDs) (5). For example, our series, as well as all cases were previously reported (37-52) with two exceptions: Quiroga and Detrol (tolterodine treatment) which is known to cause SJS (31), but Detrol (tolterodine treatment) has been identified by the Adverse Events Reporting System (AERS) of the FDA as having a Potential Signal of Serious Risk/New Safety Information related to SJS, but as of May 2011 the FDA stated that current tolterodine tartrate labeling is adequate (53).

• Two immunomodulatory/anti-inflammatory treatment strategies were used frequently in our case series, namely corticosteroids and IVIG, either alone or in combination with other immunomodulatory therapy. However, none of our patients receiving each treatment: i.e. - four supportive measures only, with four corticosteroids, with three IVIG with both corticosteroids and IVIG.

• Combined treatment had the shortest hospital stays of 2 and 8 days, but also was utilized in the case of our only fatality. However, in that case, the patient was given ongoing exposure to a potentially cross-reactive antibiotic, gatifloxacin, in the eye drops prescribed for management of the ocular involvement (case 11). Whether or not this contributed to the adverse outcome was unclear. The other case with significant morbidity (as indicated by a prolonged hospital stay of 2.5 months) was due to drug ingestion immediately being withdrawn, and the patient experiencing ongoing exposure to the offending agent (case 8). There seems to be a strong correlation between the use of supportive care, IVIG and corticosteroids otherwise.

Conclusion

• For the diagnosis of SJS, the presence of a prodrome and skin findings, but not necessarily bullae or sloughing after initiation of an agent known to cause SJS, is what averted a clinical suspicion and precipitous initiation of treatment.

• We identified two agents, Quinine and Detrol, which had not previously been linked with SJS/TEN in the peer-reviewed published literature to date.

• There seems to be little difference in terms of hospital stay between the use of supportive care, IVIG, corticosteroids or combined IVIG and corticosteroids.

References