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CLINICAL REPORT

Profile and Pattern of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in a General Hospital in Singapore: Treatment Outcomes

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, but potentially life-threatening, reactions to medications. Both conditions have significant morbidity and mortality. The aim of this study was to document the epidemiological features, aetiologies, treatment and clinical outcomes of retrospectively reviewed data of all patients with SJS or TEN treated from January 2004 to November 2010 in a general hospital. There were 18 cases of SJS, seven cases of SJS/TEN overlap and three cases of TEN. Mean age was 50.6 years, with a range of 13–85 years. The male/female ratio was 1. Drugs accounted for 26 cases; one case was caused by *Neisseria gonorrhoea* infection. Anti-convulsants (35.7%) were the most common implicated drugs followed by antibiotics (28.5%), non-steroidal anti-inflammatory drugs (NSAIDS) (14.3%), allopurinol (7.1%) and traditional Chinese medication (7.1%). In seven cases, multiple drugs were implicated. Most SJS cases (88%) were treated with corticosteroids, of which 61% were given high-dose systemic corticosteroids. No infective complications were observed. Six out of the seven SJS/TEN overlap syndrome and all three TEN cases were given intravenous immunoglobulins. One patient with TEN died. In conclusion, anti-convulsants, especially carbamazepine, were the most frequently implicated drugs, followed by antibiotics and NSAIDS. High-dose corticosteroids were effective in SJS, whereas intravenous immunoglobulin were useful in TEN and SJS/TEN overlap syndrome. *Key words: Stevens-Johnson syndrome; toxic epidermal necrolysis; Singapore*.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, but potentially fatal, disorders. They are considered to be clinical entities within a spectrum of adverse cutaneous drug reactions of increasing severity based on their surface of skin detachment (1). Bastuji-Garin et al. (2) proposed the most widely accepted consensus definition, which for SJS consists of epidermal detachment of less than 10% body surface area, for TEN epidermal detachment of more than 30% detachment, and for SJS/TEN overlap syndrome epidermal detachment of between 10% and 30%.

The reported incidence varies from 1.2 to 6 per million patient-years for SJS, and from 0.4 to 1.2 per million patient-years for TEN (3). The incidence rises with increasing age and is at least a 1,000-fold higher in patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (4).

The majority of cases of SJS and TEN are drug-induced. Other possible causes include infections, immunizations, environment chemicals and radiation therapy. The most commonly implicated drugs consist of antibiotics, anti-convulsants, non-steroidal anti-inflammatory drugs (NSAIDS) and allopurinol. With the increasing number of HIV/AIDS patients, nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) used to treat HIV-1 infection and AIDS, is the most commonly implicated drug in these patients (5).

Although rare, SJS and TEN have a significant impact on public health because of high morbidity and mortality. Mortality in SJS is generally below 5%, whereas TEN has a mortality rate of up to 30% (6).

The aim of this study is to present the epidemiological features, aetiologies, treatment and clinical outcomes of SJS and TEN in a general hospital in Singapore during a 7-year-period.

METHODS

Patients admitted between January 2004 and November 2010 with a diagnosis of SJS, SJS/TEN overlap or TEN were identified from the hospital's computer database. The case notes, charts, investigation results and treatment records of these patients were retrospectively reviewed. Data obtained included the age, gender, ethnic group, medical history, presenting complaints, inciting drugs, duration between the initial consumption of the drug and the onset of symptoms, SCORTEN score and the HLA genotyping, if it was sent. Treatment regimens, duration of hospitalization and mortality were also recorded.

There were 18 cases of SJS, seven of SJS/TEN overlap, and three of TEN, giving a total of 28 patients (Table I). Patients were in the age range 13–85 years. Mean age was 50.6 years, with a range of 13–85 years. The majority of the patients were in the age range 30–39 years, and there were an equal number of male and female patients. There were 18 Chinese patients, 9 Malay patients and one Filipino patient.

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Table I. *Patient characteristics*

Pat. No.	Diagnosis	Sex/age, years	Cause	Onset, days	Treatment	Hospital stay, days	Complications	SCORTEN
1	SJS	F/13	Paracetamol	2	Prednisolone	8	None	0
2	SJS	F/32	Naproxen	12	Prednisolone	5	None	0
3[a]	TEN	M/85	Alfuzosin	7	IVIG	11	Pneumonia, bacteraemia, acute renal failure	5
4	SJS	F/81	Ciprofloxacin	2	Prednisolone	4	Mild bilateral conjunctivitis	1
5	TEN	F/47	Carbamazepine	15	IVIG	20	Transaminitis	2
6	TEN	F/31	Cephalexin	4	IVIG	18	None	2
7	SJS	M/39	Unknown	5	Supportive	6	None	0
8	SJS	M/43	Gonorrhoea	7	Supportive	7	Transaminitis	1
9	SJS/TEN	F/47	Carbamazepine	14	Prednisolone	21	None	2
10	SJS/TEN	M/73	Carbamazepine, diclofenac, amoxicillin	7	IVIG	9	None	3
11	SJS	M/37	Aspirin	2	IV hydrocortisone	8	None	0
12	SJS	M/37	Carbamazepine	7	IV hydrocortisone	8	None	0
13	SJS	M/84	Amoxicillin/clavulanate, ceftriaxone, metronidazole, alfuzosin	42	IV hydrocortisone	7	None	1
14	SJS	M/79	Erythromycin, Allopurinol	60	IV hydrocortisone	8	Transminitis	1
15	SJS/TEN	M/50	TCM that contained phenylbutazone (NSAID)	9	IVIG	17	Transminitis	3
16	SJS	F/35	Carbamazepine	15	IV hydrocortisone	21	Symblepharon, infective keratitis	0
17	SJS	F/74	Carbamazepine	11	IV hydrocortisone	11	Transminitis	1
18	SJS	M/61	TCM	4	IV hydrocortisone	17	Reactive depression	2
19	SJS/TEN	M/55	Amoxicillin/clavulanate, Cloxacillin	3	IVIG	20	Acute renal impairment secondary to dehydration	2
20	SJS/TEN	M/15	Carbamazepine	15	IVIG	19	Neutropaenia, transaminitis	1
21	SJS/TEN	F/18	Trimethoprim-sulphamethoxazole	2	IVIG	18	Bicytopaenia, transaminitis	3
22	SJS	F/63	Trimethoprim-sulphamethoxazole, amoxicillin	17	IV hydrocortisone	6	None	1
23	SJS/TEN	F/25	Carbamazepine	11	IVIG	12	Transaminitis, subtarsal fibrosis, symblepharon, haemolytic anaemia	1
24	SJS	F/56	Allopurinol	24	IV hydrocortisone	8	Pseudomembranous conjunctivitis	1
25	SJS	M/50	Carbamazepine	16	Prednisolone	5	None	2
26	SJS	F/76	Etoricoxib	5	Prednisolone	2	None	1
27	SJS	F/76	Ceftriaxone	3	IV hydrocortisone	12	None	1
28	SJS	M/33	Carbamazepine	15	IV hydrocortisone	15	None	0

[a]This patient died.
SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; IVIG: intravenous immunoglobulins; IV: intravenous; TCM: traditional Chinese medicine.

RESULTS

Aetiologies

One patient with SJS (No. 8) had confirmed gonorrhoea infection; this 43-year-old man presented with a one-week history of targetoid rash associated with oral erosions, reactive arthritis of the left ankle and penile discharge. Genital swab isolated Gram-negative diplococci suggestive of *Neisseria gonorrhoeae*. He was treated with intramuscular penicillin. No cause was ascertained in one patient with SJS (No. 7). Drugs caused the rest of the cases. Anti-convulsants (35.7%) were the most common implicated drugs, followed by antibiotics (28.5%), NSAIDS (14.3%), allopurinol (7.1%) and traditional Chinese medication (7.1%). In seven cases, multiple drugs were implicated. Carbamazepine (CBZ) was the only anti-convulsant implicated. Beta-lactam antibiotics (5 cases) were the most frequent causative drugs among the antibiotics, followed by sulphonamides (2 cases) and fluroquinolones (1 case). The beta-lactam antibiotics implicated include amoxicillin and cloxacillin from the penicillin group, cefalexin and ceftriaxone from the cephalosporin group and co-amoxiclav (amoxicillin with clavulanic acid) from the combination group. HLA genotyping was carried out for two of our patients with carbamazepine-induced SJS/TEN. Both were positive for the HLA-B*1502 allele.

Interval between the first drug intake and onset of symptoms

The mean time-period between ingestion of the drug and onset of symptoms was 15.3 days, with a range of 2 days to 2 months. More than half (60.7%) of the patients developed symptoms within 2 weeks. Antibiotics had the shortest interval between ingestion time and onset of symptoms, of which fluoroquinolones with a mean interval of 2 days, beta-lactams with a mean interval of 4 days and sulphonamides with a mean interval of

10 days. CBZ had a mean interval of 15 days and allopurinol had a longer interval, of 42 days.

Treatment

For the SJS cases, only two cases were treated with supportive treatment without corticosteroids, five were given oral corticosteroids (prednisolone 0.5–1 mg/kg/day, which was tailed off over 2–4 weeks) and 11 were given intravenous corticosteroids (hydrocortisone 300–400 mg/day for 7–10 days). For the SJS/TEN overlap syndrome, one patient was given oral corticosteroids and six were given intravenous immunoglobulins (IVIG). All the three TEN cases were given a total of 3 g/kg IVIG over 3 days.

SCORTEN and mortality

In order to evaluate prognosis in patients with SJS/TEN, the validated SCORTEN disease severity scoring system (7) (Table II) was calculated. Seven patients had SCORTEN of 0, 11 patients had SCORTEN of 1, six patients had SCORTEN of 2, three patients had SCORTEN of 3 and one patient with a SCORTEN of 5. The latter was an 85-year-old man who received alfuzosin for his benign prostate hypertrophy. He developed pneumonia, pseudomonas bacteraemia, which was complicated by acute on chronic renal failure. He died 7 days after onset of TEN.

DISCUSSION

SJS/TEN is a rare disease. In our series, there were only 28 cases of SJS and TEN over a 7-year period. In contrast to earlier studies showing that females are affected with SJS/TEN twice as often as males (8, 9), our series had equal numbers of males and females. The demographics may have changed, however, in recent years, as HIV/AIDS patients who develop SJS/TEN are primarily men. In a recent study in a teaching hospital in Lomé, Africa, 54.6% of SJS/TEN patients were HIV-positive (10).

The most common drugs implicated in our hospital were anti-convulsants. Interestingly, CBZ is the only anti-convulsant implicated. CBZ has been reported as the most common culprit drug for SJS and TEN in several Asian countries. A strong association between HLA-B*1502 and CBZ-induced SJS/TEN has been reported in Han Chinese (11), Thai (12), Indian (13) and Malay (14) patients. The US FDA and similar regulatory agencies in Canada and Taiwan have updated the CBZ drug label to include the genetic information. Even so, Singapore doctors do not routinely screen patients for HLA-B*1502 allele before starting treatment with CBZ. We want to highlight this finding so that doctors who frequently prescribe CBZ preferably screen their patients for HLA-B*1502 allele. Hung et al. (15) carried out a case-control study and concluded that phenytoin, lamotrigine and oxcarbazepine, which possess an aromatic ring like that of CBZ, share a common risk allele. They suggest that aromatic anti-epileptic drugs should be avoided in the B*1502 carrier and caution should also be exercised for lamotrigine.

Table II. *SCORTEN*

Risk factor	0	1
Age (years)	<40	>40
Associated malignancy	No	Yes
Heart rate (beats/min)	<120	>120
Serum blood urea nitrogen (BUN) (mg/dl)	<27	>27
Detached or compromised body surface (%)	<10	>10
Serum bicarbonate (mEq/l)	>20	<20
Serum glucose (mg/dl)	<250	>250

In Europe and Israel, allopurinol is the most common cause of SJS and TEN. Daily doses equal to or greater than 200 mg were associated with a higher risk. The risk was restricted to short-term use (≤8 weeks) (16). While the HLA-B*1502 allele is absent in the Caucasian (17) and Japanese population (18), HLA-B*5801 is strongly associated with allopurinol-induced SJS/TEN in the European (19), Japanese (18), Han Chinese (20) and Thai populations (21).

The mean number of days between ingestion of the drug and onset of symptoms for our patients was 15 days. This is consistent with the typical interval, which is between 1 and 3 weeks. For many drugs, the risk of SJS and TEN was highest in the first weeks of use, particularly for antibiotics, as shown in our study. For most high-risk drugs that are intended for long-term use, the risk of developing SJS or TEN is elevated during the initial 2 months of use (6, 22).

To date, the pathogenesis of SJS and TEN is still not fully understood. SJS and TEN are characterized by massive keratinocyte apoptosis. Fas-Fas ligand (FasL)-induced apoptosis in keratinocytes is one of the most thoroughly studied immune mechanisms in SJS/TEN. It was first proposed in 1998 that the death receptor Fas/CD95 plays a key role in the apoptosis of keratinocytes that leads to epidermal necrolysis (23). However, inconsistent findings of Fas, FasL and soluble FasL (sFasL) brought into question the original hypothesis from Viard et al. (23). Subsequently, numerous possible mediators of keratinocyte apoptosis have been suggested, such as peripheral cytotoxic T cells (18), inflammatory cytokines (24), nitric oxide (25), granzyme B (26), perforin (27) and granulysin (28). The strong associations of HLA-B*1502 with CBZ-induced SJS/TEN and HLA-B*5801 with allopurinol-induced SJS/TEN also suggested that genetic predisposition plays a role in the pathogenesis of SJS/TEN.

Currently, no treatment modality has been established as standard for these patients. Due to the rarity of these disorders, there are no randomized controlled

trials of pharmacological agents in the treatment for SJS and TEN. However, there are case reports of successful treatment using IVIG, systemic corticosteroids, plasmapheresis, cyclosporine, cyclophosphamide, anti-tumour necrosis factor-α (TNF-α) and haemodialysis (29).

The controversy over whether systemic corticosteroids should be used to curtail progression remains unresolved. For example, in Germany, corticosteroids are used in 80% of cases of SJS, whereas in France, systemic corticosteroids are used in only 20% of such patients (30). The corticosteroids therapies that were reported to reduce morbidity and improve outcome of SJS/TEN patients includes oral prednisolone, intravenous hydrocortisone, pulsed intravenous methylprednisolone (31) and pulsed intravenous dexamethasone therapy (32).

Out of our 18 patients with SJS, 16 were given corticosteroids, of which 11 were given intravenous hydrocortisone. No complication of sepsis was observed in these patients. It appears reasonable to initiate corticosteroids as acutely as possible before significant tissue damage has occurred, or later if the disease is still in its progressive stage. They should be used in combination with antiviral or antimicrobial agents in case of an underlying infectious aetiology.

IVIG contains anti-Fas antibodies that can abrogate the Fas-mediated keratinocyte apoptosis (23). Most studies on IVIG in SJS and TEN reported improvement in arresting disease progression and reduction in time to skin healing (33–35). In general, mortality varied from 0% to 12% in studies that supported the use of IVIG, and 25% to 41.7% in those that did not demonstrate a beneficial effect (36–38). Mortality was associated with a lower dose of IVIG, longer time of onset before IVIG use, co-existing underlying chronic conditions, older age and greater body surface area involved.

In our case series, six out of the seven cases with SJS/TEN overlap syndrome and all three TEN cases were given IVIG. They were given a total of 3 g/kg IVIG over 3 days. Previous studies that used lower dose of IVIG (2 g/kg total dose) reported an increase in mortality (37, 38). All our patients who were given IVIG were admitted to the intensive care unit, where they were monitored closely. The mean length of stay for these patients was 16.9 days. Only one patient with TEN died of pneumonia, pseudomonas bacteraemia and acute on chronic renal failure. None of the patients in our series experienced adverse events related to IVIG, such as anaphylaxis and acute renal failure. We recommend a total dose of 3 g/kg IVIG.

Our experience leads us to conclude that steroid therapy with high-dose corticosteroids is effective in SJS, whereas IVIG is effective in TEN. However, multicentre, randomized, placebo-controlled trials using a standardized design are needed to validate these findings.

The authors declare no conflict of interest.

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