Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: a Review of Fourteen cases.

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Abstract P8

• **Background:** Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are the most severe drug-induced cutaneous reactions. Diagnosis is clinical, with no specific criteria, and there are no universally accepted standards of care. A retrospective case series will bring further evidence towards establishing standards of diagnosis and treatment.
• **Methods:** Eight year retrospective case series evaluation of electronic medical records of patients seen at Kingston General Hospital with ICD-9 codes of Bullous Erythema Multiforme, TEN and Unspecified Erythema Multiforme. Patient sex, age, inciting agent, symptoms, management strategies, duration of illness, and outcomes were recorded for qualitative and descriptive analysis.
• **Results:** 95 charts were returned from which 14 SJS and 0 TEN cases were found. There were 5 female and 9 male patients. Average age was 51.4 years. All cases but one were drug-induced. A prodrome was recorded in 10 cases. Six cases had eruptions typical of SJS (progressing to vesicles/bullae and skin sloughing). Mucosal involvement was present in all cases. All diagnoses were made on clinical grounds, with three confirmed by biopsy. Combination treatment (IVIG and corticosteroids) was implemented in 3 patients, 3 were treated with IVIG alone, 4 with corticosteroids alone, and 4 with only supportive therapy. Hospital stay ranged from 2 to 65 days, with all but 2 patients hospitalized for less than two weeks. One case was fatal. Nature of therapy did not appear to influence length of stay or complications. A prodrome illness with skin findings, not necessarily classic for SJS appearing shortly after a novel medication introduction aroused clinical suspicion for diagnosis. Two culprit agents, Quinine and Detrol, were not previously linked with SJS in the medical literature.
• **Conclusion:** SJS/TEN remains a relatively rare complication of drug therapy with only 14 cases identified in our centre over the previous 8 years. There was little difference in hospital stay comparing supportive care to IVIG, corticosteroids or combined therapy treatments.

Background

• Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are the most severe of a large spectrum of drug-induced cutaneous reactions (1). They are as differing spectrums of the same disorder, with SJS being less severe (2,3).

• SJS is characterized by a prodrome of fever, malaise and myalgias with subsequent eruption of erythematous or purpuric macules and plaques which progress into vesicles and bullae. Disease progression culminates in epidermal death and sloughing of 10% or less of the body surface area (BSA), and includes at least two mucosal surfaces (ocular, oral, genital). TEN presents with a more severe prodrome that includes skin pain and fever as high as 39ºC, 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. The incidence of SJS and TEN is estimated at 2 cases/million/year, with SJS outnumbering TEN by approximately 3-fold (4-6).

• No laboratory tests that will confirm a definitive diagnosis of SJS/TEN (7); Diagnosis is based solely upon clinical history and examination (8).

•Basic principles of treatment are removal of the offending agent, and administration of supportive care(9,10). Beyond this, there is no universally accepted standard treatment for SJS/TEN (11). Short term, high dose systemic corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis yield mixed results(12-21).

• 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 generally accepted gold standards of treatment (23).

Objective

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

Methods

• Retrospective case series evaluation of electronic medical records of patient 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), L511 Bullous Erythema Multiforme, L512 Toxic Epidermal Necrolysis and L519 Unspecified Erythema Multiforme(EM).

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

Results

Table 1. Descriptive Values of Charts

ICD-9 or Equivalent Code	Number of Charts Returned	Charts available	Cases of Diagnosed SJS or TEN
Bullous Erythema Multiforme (BEM)	24	19	14
Toxic Epidermal Necrolysis (TEN)	2	2	0
Unspecified Erythema Multiforme (UEM)	69	41	0

• Mean age of patients was 51.4 years (27 to 82); 35.7% were female
• All cases but one were drug-induced
• Average time from initiation of the culprit agent to onset of eruption was 15 days (range 1 to 34 days, excluding case 3, where the patient had been taking allopurinol for many years).
• Ten patients had had a documented prodrome
• Six of fourteen cases had eruptions typical of SJS in which the eruption progresses to vesicles/bullae and skin sloughing (cases 2,5,6,10,11,14), whereas five did not (cases 1,3,7,9,13) and in three there was not an adequate description of the eruption (cases 4,8,12).
• Mucosal involvement was present in all cases, with six cases involving one, six cases involving two, and one case involving three mucosal surfaces. Average hospital stay was 12 days.

• Combination treatment with IVIG and corticosteroids was implemented in three patients, three were treated with IVIG alone, four with corticosteroids alone, and four with only symptomatic/supportive therapy. All but one patient survived. Hospital stay ranged from two to 65 days, with all but two patients hospitalized for less than two weeks.

Table 2. Summary of SJS Cases

Case	Age /Sex	Inciting Agent/ Time prior to presentation	Prodrome	Eruption Description	Mucosal Surfaces Involved	Management/Outcome/ Hospital Stay in Days
1	45/f	Azithromycin/1d	Muscle aches, joint stiffness, no fever	Dark macules within pruritic erythemata over entire body excluding palms and feet, no desquamation	Oral, ocular	IV hydrocortisone, IVIG x 4 days, IV diphenhydramine, oral lidocaine rinse/survived/2
2	32/f	TMP-SMX/15d		Diffuse maculo-papular rash with blisters covering 70% of body, about 5-10% epidermal sloughing	Oral, ocular	IV hydrocortisone, IVIG x 1 dose, oral lidocaine rinse, ocular erythromycin, lubrication/survived/8
3	64/m	Allopurinol/8y	Fever, chills, malaise, arthralgias	Painless erythema beginning on soles/palms, spreading to abdo, buttock, chest, and evolving to maculopapular eruption with target lesions with central pustule	Oral	IVIG x 3 days/survived/15
4	75/m	Hydroxychloroquine	Fever	"Stevens-Johnson Syndrome-like" *	Oral	IV, then oral corticosteroids/ survived
5	27/m	Carbamazepine/7d	Fever, diarrhea, syncope	Pruritic/painful eruption beginning on face and torso, spread to rest of body in few days, blisters on palms	Oral, ocular	Dimenhydrinate, diphenhydramine, acetaminophen/survived
6	67/m	Quinine	fever, arthralgia, cough, chills	Maculopapular eruption beginning on the arm, spreading to trunk, became darker, spread to elbows/knees, then developed pustules in area of rash, evolved to dark red/purple macules, papules and bullae with raised borders, some crusted and erythema with purple centers present on arms, trunk, legs, feet	Oral	oral prednisone, oral xylocaine rinse/survived/28
7	27/f	Unknown		Periorbital swelling and crusting, followed by a pruritic rash on trunk and arms, spreading to the abdomen and legs, evolving to macules/target lesions,	Oral, ocular, genital	IVIG x 4 days, prednisolone eye drops, ocuflox drops, celluvisc drops, warm eye compresses, ocular erythromycin, oral benzydamine hydrochloride mouthwash/survived/10
8	27/m	Lamotrigine		Healing desquamation on face, torso, back, arms, legs (initially "full body rash" incorrectly diagnosed as tinea corporis, developed secondary cellulitis, then transferred to KGH).		None (SJS resolved)/survived, hospitalized for 2.5 months due to initial misdiagnosis, continuation of lamotrigene and development of cellulitis
9	29/m	Clarithromycin/4d		Fine macular rash on body sparing palms, soles, scalp, erythematous rash dorsum of feet, back of neck	Oral, ocular	diphenhydramine, acetaminophen prednisolone 1%, gatifloxacin eye drops, analgesic mouthwash/ survived/13
10	77/m	Coricidin/1d vs Allopurinol/years	fevers, chills, "cold-like" symptoms prior to taking coricidin	Bullae on back, perineum, subsequently developed erythema on back, chest, abdo, penis, perineum, and present blisters ruptured, less than 10% epidermal sloughing	Genital	None/survived
11	67/m	Moxifloxacin/7d	Fever, weakness, "flu-like" symptoms	Diffuse erythematous macules, no ulcers/scaling, no target lesions, progressed to sloughing of skin on arms, legs, scrotum	Ocular	IV corticosteroids, IVIG, 3 ophthalmic amniotic membrane grafts, gatifloxacin eye drops/expired.
12	82/f	Detrol/25d	Sore throat, headache	Pruritic erythema on legs, arms "clinically suggestive of SJS"	Oral	Oral prednisone/survived/14
13	69/m	Phenytoin/34d vs Valproic Acid/25d	Fever, fatigue, weakness, nausea, vomiting, urinary urgency/frequency	Erythematous macules on scalp, face, chest, no desquamation.	Oral, ocular	IVIG x3 days, ocular refresh tears, tear gel/survived/9
14	36/f	Phenytoin /28d vs Valproic Acid/28d	Fever, chills, night sweats, anorexia, weight loss, facial,leg edema, lymphadenopathy	Pruritic erythematous macular rash on feet, spreading to the whole body, multiple small blisters, skin sloughing on toes	Oral, genital	IV methylprednisolone followed by oral prednisone/survived

* Limited chart notes. This statement or similar are the only descriptions of the reaction found.

Discussion

• SJS/TEN are frequently misdiagnosed and underreported because lesions are initially nonspecific especially in the early stages of the reaction, and multiple conditions can cause desquamation (8,24).

• In our series, all patients obtained their diagnosis on clinical grounds, although four had skin biopsies performed (cases 6,8,10,11), three diagnosed as SJS (cases 6,8,11), and one reported as "nonspecific inflammation." Clinical diagnosis seemed to rely on prodromal features, skin and mucosal involvement as well as recent exposure to a new medication rather than depending on the classical skin lesions of SJS, which includes epidermal necrosis and skin sloughing (3,4). Indeed, only six of our fourteen cases presented with bullae and skin sloughing. It can be hypothesized that based on a quick clinical diagnosis and administration of treatment, the later stages of cutaneous progression may have been avoided. There were only two appearances of the commonly associated targetoid lesions (cases 3,7).

• Literature review indicates that the most commonly implicated medications include antibiotics (sulfonamides predominating), allopurinol, anti-convulsant medications (namely carbamazepine, lamotrigine, dilantin, and phenobarbital) and non-steroidal anti-inflammatory drugs (25-27). In this case series, all causative agents were previously reported (27-32)) with two exceptions: Quinine and Detrol (tolterodine tartrate). Quinine is not known to cause SJS (33), but Detrol (tolterodine tartrate) 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 the current Tolterodine tartrate labeling is adequate and that no further regulatory action is needed at this time (34).

• Two immunomodulatory/anti-inflammatory treatment strategies were used frequently in our case series, namely corticosteroids and IVIG, either alone or in combination. There was roughly an even number of patients receiving each treatment: i.e. - four supportive measures only, four with coritcosteroids, three with IVIG and three 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 their condition initially being misdiagnosed as tinea corporis, and the patient experienced ongoing exposure to the offending agent (case 8). There seems to be little difference 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 aroused a high 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

1. Dermatologica Sinica 2009; 27(4):203-209.
2. J Dermatol 1997; 24:726.
3. J Am Acad Dermatol 1985; 13:623.
4. Arch Dermatol 1993; 129:92
5. J Clin Epidemiol 1996; 49:769.
6. Br J Dermatol 1996; 135:6.
7. Dent Clin N Am 2005; 49:67-76.
8. Semin Cutan Med Surg 2007; 26:147-154.
9. Arch Dermatol 2000; 136:323.
10. J Burn Care Rehabil 2002; 23:87
11. Ann Allergy Asthma Immunol 2006; 97:272. J
12. Burn Care Rehabil 1997;18:520–4.
13. Int Ophthalmol Clin. 2005;45:25–48.
14. Allergy Proc. 1992;13:89–95.
15. Allergy Asthma Proc. 2000;21:101–5.
16. J Dermatol. 1999;26:718–22.
17. Ann Surg. 1986;204:503–12.
18. J Burn Care Rehabil. 1997;18:520–4.
19. Dermatology 2003; 207:96.
20. Drugs 2005; 65:2085.
21. Intensive Care Med 1999; 25:1307.
22. Fitzpatrick's dermatology in general medicine 6th edition 2003. p.544
23. Ann Allergy Asthma Immunol 2005; 94:419.
24. Mayo Clin Proc. 2006;81:945–8.
25. Arch Dermatol 1991; 127:839.
26. J Rheumatol 2003; 30:2234.
27. Indian J Dermatol Venereol Leprol 2005; 71:325.
28. N Engl J Med 1994; 331:1272.
29. N Engl J Med. 1995 Dec 14;333(24):1600-7.
30. Acta Dermatovenerol Croat. 2006;14(1):40-5.
31. Rheumatology (Oxford). 2002 Apr;41(4):473-4.
32. Can J Clin Pharmacol. 2005 Fall;12(3):e264-8.
33. Drug Saf. 2004;27(1):25-61.
34. US Department of Health & Human Services, US Food and Drug Administration. Potential signals of serious risks/new safety information identified from the Adverse Event Reporting System (AERS) between October-December 2008