TOXIC EPIDERMAL NECROLYSIS SYNDROME: MANAGEMENT AND OUTCOMES

NÉCROLYSE ÉPIDERMIQUE TOXIQUE: PRISE EN CHARGE ET ÉVOLUTION

Al-Benna S.✉

Division of Plastic Surgery, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates

SUMMARY. Toxic epidermal necrolysis syndrome (TENS) is a rare medical emergency associated with high morbidity and mortality. At present, there is no agreement regarding specific treatments for this disease. The aim of this study is to determine the outcome of patients with TENS using a treatment protocol that did not include the use of intravenous immunoglobulin or systemic steroids. This is a retrospective study of all patients diagnosed with TENS admitted to a tertiary burns centre from 2015-2017. Twelve cases were identified with a mean age of 46±8 years. Mean total body surface area affected was 51±9%. The SCORTEN index was 3.4±0.3 (range 2-5) and predicted 3 deaths in this cohort. Overall mortality was 25%. This study casts no doubt on the prognostic validity of SCORTEN. No specific TENS treatment has been unequivocally proven to be effective.

Keywords: epidermal necrolysis, toxic, outcome assessment (health care)

RÉSUMÉ. *La nécrolyse épidermique toxique (NET) est une urgence médicale rare, grevée de fortes morbidité et mortalités. Aucun consensus ne se dégage actuellement concernant un traitement spécifique. Cette étude avait pour but d'évaluer l'évolution des patients souffrant d'une NET n'ayant reçu ni corticothérapie (CCT) ni immunoglobuline (Ig). Cette étude rétrospective concerne tous les patients (12) hospitalisés dans un CTB français pour NET entre 2015 et 2017. Ils étaient âgés en moyenne de 46 +/- 8 ans, atteints sur 51 +/- 9% de leur SCT. Le SCORTEN était de 3,4 +/- 0,3 (2 à 5) ce qui prédisait 3 morts ce qui a correspondu à la réalité et valide donc sa véracité. Aucun traitement spécifique n'a prouvé d'efficacité indubitable.*

Mots-clés : *nécrolyse épidermique toxique, soins, évolution*

✉ Correspondence to: Sammy Al-Benna, Division of Plastic Surgery, Sheikh Khalifa Medical City, PO Box 51900, Karamah Street, Abu Dhabi, United Arab Emirates. Tel.: +971 2 819 2147; email: sab@instituteofsurgery.org
Manuscript: submitted 18/09/2020, accepted 14/10/2020

Introduction

Toxic epidermal necrolysis syndrome (TENS) is a rare and severe cutaneous condition characterised by epidermal loss, and may have associated extracutaneous and systemic manifestations.[1,2] It is considered a medical emergency characterised by high fever and confluent erythema followed by necrolysis, and may be life-threatening.[1,2] It is considered to be part of a spectrum of epidermolytic adverse cutaneous drug reactions.[1,2] TENS is differentiated from Stevens-Johnson syndrome (SJS) by the amount of total body surface area (TBSA) affected, with greater than 30% TBSA affected in TENS.[1,2] In this condition, keratinocytes undergo apoptosis in an unregulated fashion.[3] The consequence of this abnormal process is widespread epidermal detachment, which may be life threatening.[3] Typically, the causative agent is a drug, although other causes have been described, including bacterial and viral infections.[3]

The incidence of TENS is between 0.4-1.2 cases per million people per year and carries a mortality of 20-40%.[1-26] Regional differences in drug prescription, the genetic background of patients (human leucocyte antigens (HLA) and metabolizing enzymes), the coexistence of cancer, or concomitant radiotherapy, can impact upon incidence.[2,3] The mean reported age of patients presenting with TENS varies from 46 to 63 years.[1-26]

At present, there is no agreement regarding specific systemic treatments for this disease. The aim of this study was to determine clinical outcomes and mortality of patients with TENS, treated at a tertiary burns centre, using a treatment protocol that did not include the use of intravenous immunoglobulin or systemic corticosteroids.

Materials and methods

This is a retrospective study of all patients diagnosed with TENS admitted to the tertiary burns centre of Sheikh Khalifa Medical City, Abu Dhabi, from 1st January 2015 to 30th June 2017. Data are presented as means ± SEMs. The following details were recorded: duration of the rash, drug intake, time period between drug intake and appearance of the rash, systemic symptoms, extent of epidermal necrosis or detachment, mucosal involvement and systemic evaluations. Diagnosis was made according to criteria laid down by Bastuji-Garin et al.[15] Drug(s) taken within four weeks preceding the onset of symptoms were considered as "culprit drugs". If the patient had taken more than one drug, all were considered as culprit drugs. Treatment was administered in the tertiary burns centre according to a local multidisciplinary care protocol. All patients were given barrier nursing care, including regular monitoring of vital signs, fluid and electrolyte balance, strict asepsis, sterile dressings and nutrition. Antibiotics were only administered to address established infection. Intravenous immunoglobulin (IVIg) and corticosteroids were not part of the treatment protocol and were not used in any patients. All patients were under shared care of burns surgeons and dermatologists and care and management were discussed at regular multidisciplinary team meetings. To allow objective evaluation of the results, an independently validated prognostic indicator, the SCORTEN (SCORing TEN) index, was calculated.[16] The study received approval from the local human research ethics committee (Ethics Approval Reference Number: REC-14.10.2015 [RS-396]).

Results

A total of 12 patients were identified during the study period, of which 6 were male. The mean age was 46±8 years. All cases of TENS were caused by drugs. The encountered causative drugs were beta-lactam antibiotics (75%) followed by cefuroxime (8%), diclofenac (8%), lansoprazole (8%) and rofecoxib (8%). The mean duration of cutaneous eruption was 7±3 days. The mean period between initial intake of the culprit drug and onset of eruption was 19±4 days. Ten patients had prodromal symptoms in the form of fever, cough, sore throat and headache. Two patients had pre-existing epilepsy, one patient had an intracranial tumour and one patient had systemic lupus erythematosus. All patients were classified as TENS. The cutaneous findings on admission were denudation (100%), bullae (83%), skin tender-

ness (75%), mucositis (67%) and purpura in dependent areas (17%). A positive Nikolsky sign was recorded in 83% patients. There was extensive loss of skin, with a mean 51±9% total body surface area affected. All patients had involvement of either oral (75%), ocular (58%) or genital (50%) mucosa. The SCORTEN index was calculated in all patients (median SCORTEN 3, range 2-5). The SCORTEN predicted 3 deaths in this cohort. The overall mortality was 3/12 (25%). The mean duration of hospitalisation was 18±6 days for survivors.

Discussion

TENS continues to represent a challenge for medical and surgical management and has a high associated mortality.[1,2] No patient in this series received IVIG or corticosteroids. This study contends that the best results in TENS are obtained with treatment in a tertiary burn centre with burns surgeons, intensivists, dermatologists and infectious disease specialists on the management team.[17-19]

TENS is considered an idiosyncratic drug reaction in 95% of published cases.[2-16] In this series, all cases were attributed to a single drug based on clinical and chronological criteria, in agreement with literature.[2-16] Antibiotics, mainly beta-lactams, were the agents most frequently involved in this series. Similar findings were noted by groups in Australia and the United Kingdom.[4,5] This contrasts with evidence from Asia, where anticonvulsant drugs have been implicated as the most common causative agents.[10] It also differs with findings from France, which suggested non-steroidal anti-inflammatory drugs were the most commonly involved culprits.[7] However the European Study of Severe Cutaneous Adverse Drug Reactions (EuroSCAR) study, a prospective case-control study conducted in six countries (Austria, France, Germany, Israel, Italy and the Netherlands), identified allopurinol as the most common cause of TENS, particularly when administered in high doses.[13] Similar findings were noted by a group in Tunisia.[2] In agreement with American, French and Tunisian data, we observed the occurrence of TENS cases predominantly in the 5th decade of life (mean 46±8 years).[2,7,9,11] This differs from the 7th decade of life, observed in Australian, German and Portuguese studies.[1,5,8] All patients in the present study gave a history of drug intake prior to the onset of skin pathology. French and German studies reported a small number of patients (4.5 and 3%, respectively) with TENS who did not have any history of drug intake preceding onset.[7,9]

Admission delay to the tertiary burn centre was 7±3 days, more than double that of other studies, corresponding to a very late referral and thus a delayed start of supportive and therapeutic care, even though most cases were admitted as tertiary level transfers rather than from hospital Emergency Departments.[4,15] In addition, suspension of the causative drug was also belated (19±4 days). Together, these two points reflect delays in diagnosis, possibly due to the condition's rarity and non-specific initial clinical features, suggesting medical education may have an important role to play in attempts to improve outcomes from TENS.

The reported mortality rate in the largest series of patients with TENS was found to be 28.6%.[13] In this present study, the mortality rate was 25%. The roles of systemic steroids and IVIg in TENS remain controversial and further large-scale studies will be required to establish their true usefulness or otherwise.[3] No patient in this series received either intervention, and the observed mortality was in keeping with that of published series which have included patients treated in this way.[13]

SCORTEN is a scoring system which is used to stratify gravity and estimate mortality in certain bullous conditions.[16] It was originally developed for toxic epidermal necrolysis, but can be used with burn victims, sufferers of Stevens-Johnson syndrome/toxic epidermal necrolysis, cutaneous drug reactions, or exfoliative wounds. These conditions have in common that they compromise the integrity of the skin and/or mucous membranes. In the SCORTEN scale, 7 independent risk factors for high mortality are systematically scored (*Table I*). The SCORTEN includes independent risk factors of equal weight, so as to determine the mortality rate for that particular patient: age of 40 years or older; heart rate of 120 beats per minute or more; cancer/hematologic malignancy; involved body sur-

Table I - SCORTEN severity of index score for Stevens-Johnson syndrome/toxic epidermal necrolysis

Risk factor	0	1
Age (years)	<40	≥40
Associated malignancy	No	Yes
Heart rate (beats/min)	<120	≥120
Serum urea level (mmol/L)	<10	≥10
Percentage of epidermal detachment	<10%	≥10%
Serum bicarbonate (mmol/L)	≥20	<20
Serum glucose (mmol/L)	<14	≥14

The mortality risk depends on the score: SCORTEN 0-1 > 3.2%; SCORTEN 2 > 12.1%; SCORTEN 3 > 35.3%; SCORTEN 4 > 58.3%; SCORTEN 5 or more > 90%.[16]

face area (BSA) greater than 10%; serum urea greater than 10 mmol/L; serum bicarbonate less than 20 mmol/L; and serum glucose greater than 14 mmol/L. Each variable contributes 1 point to the overall score if present. The more risk factors present, the higher the SCORTEN score, and the higher the mortality rate. The SCORTEN was developed and prospectively validated to be calculated at the end of the first 24 hours of admission, for this calculation using the total body surface area of detached and detachable epidermis affected at that time, and the most abnormal values during the first 24 hours of admission for the other variables. On the basis of the original study, a SCORTEN of 0 to 1 corresponds to a mortality rate of 3.2%, 2 to 12.1%, 3 to 35.3%, 4 to 58.3%, and 5 or greater to 90.0%.[16] Its application in TENS patients treated in burn units has been called into question by some authors who argue that SCORTEN overestimates mortality, since it was initially endorsed from a group with less severe forms of the disease.[27] In this small series, SCORTEN displayed 100% sensitivity and 100% specificity as a prognostic tool.

Early administration of high-dose IVIg has been suggested as a means to achieve early resolution and reduced mortality,[10] however opinions on this vary.[11] The use of systemic steroids is also controversial.[3,11] Comparison of 15 patients with TEN managed without steroids with a group of 15 receiving high doses (240–1000 mg hydrocortisone) daily found improved survival in the non-steroid-treated group (66% vs. 33% in the steroid-treated group).[12] In contrast, extracted results from the EuroSCAR study noted that patients receiving corticosteroids had a less severe disease course compared with those receiving IVIg or supportive care only, suggesting a potential benefit from steroids.[13]

Conclusion

Overall mortality in this series was 25%. These results are consistent with other large multicentre publications.[6,13] SCORTEN was highly accurate in predicting mortality. TENS' pathophysiology is still not clear and a specific treatment has not yet been identified.[3] The findings from this series and previous studies suggest that best outcomes may be achieved by early diagnosis and immediate transfer to a burns unit, with burns surgeons, intensivists, dermatologists and infectious disease specialists on the management team.[13-16] Given the known incidence and lack of specific drug treatments, there is a clear need for a national, or international, multi-centre study on the use of IVIg and systemic corticosteroids in the management of TENS.[28-31]

BIBLIOGRAPHY

1 Barreiro D, Monteiro D, Isabel O, Silva A et al.: Twelve years of Lyell's Syndrome in the burn unit of São João Hospital Centre. Ann Burns Fire Disasters, 31: 259-265, 2018.

2 Mokline A, Rahmani I, Garsallah L, Tlaili S et al.: La nécrolyse épidermique toxique. Ann Burns Fire Disasters, 29: 37-40, 2016.

3 Harris V, Jackson C, Cooper A: Review of toxic epidermal necrolysis. Int J Mol Sci, 17: 2135, 2016.

4 Rajaratnam R, Mann C, Balasubramaniam P, Marsden JR et al.: Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary centre. Clin Exp Dermatol, 35: 853-62, 2010.

5 Wong KC, Kennedy PJ, Lee S: Clinical manifestations and outcomes in 17 cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Australas J Dermatol, 40: 131-4, 1999.

6 Guillaume JC, Roujeau JC, Revuz J, Penso D, Touraine R: The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). Arch Dermatol, 123: 1166-70, 1987.

7 Roujeau JC, Guillaume JC, Fabre JP, Penso D et al.: Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. Arch Dermatol, 126: 37-42, 1990.

8 Schöpf E, Stühmer A, Rzany B, Victor N et al.: Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. Arch Dermatol, 127: 839-42, 1991.

9 Halebian PH, Corder VJ, Madden MR, Finklestein JL et al.: Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg, 204: 503-12, 1986.
10 Zhu QY, Ma L, Luo XQ, Huang HY: Toxic epidermal necrolysis: performance of SCORTEN and the score-based comparison of the efficacy of corticosteroid therapy and intravenous immunoglobulin combined therapy in China. J Burn Care Res, 33: e295-308, 2012.
11 Bachot N, Revuz J, Roujeau JC: Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol, 139: 33-6, 2003.
12 Halebian PH, Corder VJ, Madden MR, Finklestein JL et al.: Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg, 204: 503-12, 1986.
13 Schneck J, Fagot JP, Sekula P, Sassolas B et al.: Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol, 58: 33-40, 182, 2008.
14 Gerdts B, Vloemans AF, Kreis RW: Toxic epidermal necrolysis: 15 years' experience in a Dutch burns centre. J Eur Acad Dermatol Venereol, 21: 781-8, 2007.
15 Bastuji-Garin S, Rzany B, Stern RS, Shear NH et al.: Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol, 129: 92-6, 1993.
16 Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC et al.: SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol, 115: 149-53, 2000.
17 Concannon E, Kennedy S, Shelley O: Toxic epidermal necrolysis after acute burn injury. Ann Burns Fire Disasters, 31: 266-270, 2018.
18 Bazine A, Fetohi M, Namad T, El Benaye J et al.: Toxic epidermal necrolysis in a female with metastatic breast cancer treated with vinorelbine. Ann Burns Fire Disasters, 30: 261-263, 2017.
19 Lipový B, Rihová H, Kaloudová Y, Mager R et al.: Use of XeDerma(®), a novel biological cover, in a female patient with toxic epidermal necrolysis. Ann Burns Fire Disasters, 27: 136-140, 2014.
20 Yapici AK, Fidanci MK, Kilic S, Balamtekin N et al.: Stevens-Johnson Syndrome triggered by a combination of clobazam, lamotrigine and valproic acid in a 7-year-old child. Ann Burns Fire Disasters, 27: 121-125, 2014.
21 Voltan A, Azzena B: A case of toxic epidermal necrolysis (ten) with severe chronic ocular complications in a healthy 46-year-old woman. Ann Burns Fire Disasters, 23: 81-87, 2010.
22 Castana O, Rempelos G, Anagiotos G, Apostolopoulou C et al.: Stevens-Johnson syndrome: a case report. Ann Burns Fire Disasters, 22: 147-151, 2009.
23 Siah S, Baite A, Bakkali H, Atmani M et al.: Prise en charge du syndrome de Lyell ou necrolyse epidermique toxique. Ann Burns Fire Disasters, 22: 142-146, 2009.
24 Napoli B, D'Arpa N, D'Amelio L, Chimenti S et al.: Staphylococcal scalded skin syndrome: criteria for differential diagnosis from Lyell's Syndrome. Two cases in adult patients. Ann Burns Fire Disasters, 19: 188-191, 2006.
25 Elkharaz S, Abdel-Razek EM, Eldin A, Abdel-Razek AM: Severe bullous skin diseases: analysis of seven children managed in a burns unit. Ann Burns Fire Disasters, 19: 180-187, 2006.
26 Castana O, Makrodimou M, Michelakis D, Tsandoulas Z et al.: Diseases mimicking a burn - outcome and treatment. Ann Burns Fire Disasters, 18: 130-132, 2005.
27 Imahara SD, Holmes JH 4th, Heimbach DM, Engrav LE et al.: SCORTEN overestimates mortality in the setting of a standardized treatment protocol. J Burn Care Res, 27: 270-5, 2006.
28 Al-Benna S: A discourse on the contributions of evidence-based medicine to wound care. Ostomy Wound Manage, 56: 48-54, 2010.
29 Al-Benna S: Construction and use of wound care guidelines: an overview. Ostomy Wound Manage, 58: 37-47, 2012.
30 Al-Benna S, Alzoubaidi D, Al-Ajam Y: Evidence-based burn care. An assessment of the methodological quality of research published in burn care journals from 1982 to 2008. Burns, 36: 1190-5, 2010.
31 Al-Benna S, Al-Ajam Y, Way B, Steinstraesser L: Descriptive and inferential statistical methods used in burns research. Burns, 36: 343-6, 2010.

Support the International Association for Humanitarian Medicine Chisholm-Gunn

www.iahm.org