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CLINICAL REPORT

Toxic Epidermal Necrolysis: Analysis of Clinical Course and SCORTEN-based Comparison of Mortality Rate and Treatment Modalities in Korean Patients

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Toxic epidermal necrolysis (TEN) is a rare, life-threatening, drug-induced cutaneous reaction. We herein report our experience regarding causes, clinical course, treatment and sequelae of TEN in Korean patients. In addition, we used the SCORTEN, a severity-of-illness score for TEN, to compare the predicted and actual mortality rates, and to evaluate the efficacy of treatment modalities. A retrospective study of 38 patients with TEN during a 13-year period (1990–2003) at the Asan Medical Center was performed. The mean involved body surface area was 49±17%. All except three cases were associated with medications, most commonly antibiotics, followed by non-steroidal anti-inflammatory drugs, acetaminophen and herbal remedies. Fourteen patients had a history of current infection, including upper respiratory infection, pneumonia and herpes simplex infection. The mean time from initial drug administration to the onset of TEN was 9.8±5.7 days. Twenty-one patients were treated with systemic corticosteroids. Fourteen received high dose intravenous immunoglobulin therapy. The actual mortality rate was 23.7% (9/38), not significantly different from the SCORTEN-predicted rate (25.5%, 9.699/38). Also based on SCORTEN, treatment with high dose intravenous immunoglobulin showed a trend to lower actual mortality than predicted mortality (standardized mortality ratio (SMR)=0.425; 95% CI, 0.011–2.368), whereas corticosteroid therapy showed no such difference (SMR=1.004; 95% CI, 0.369–2.187). ***Key words: toxic epidermal necrolysis; SCORTEN.***

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Toxic epidermal necrolysis (TEN) was first described in 1956 in four patients with scalded skin appearance due to drugs, infections or other unknown causes (1). TEN is characterized by extensive detachment of the epidermis undergoing full-thickness necrosis (2, 3). The disease usually begins with non-specific symptoms, such as fever, cough, sore throat and burning eyes, which are followed in 1–3 days by lesions in the skin and mucous membranes (Fig. 1). A painful rash starts usually on the face and upper trunk and spreads rapidly (2, 3). Systemic involvement is common in TEN (4).

Many factors have been proposed as causes of TEN, including adverse reactions to drugs, infections, malignant disorders and graft-versus-host disease (2–5). Most case reports and studies, however, suggest that TEN is usually an idiosyncratic hypersensitivity to medication (6, 7). In a recent study from Taiwan, a strong association between HLA-B*1502 and Stevens-Johnson syndrome/TEN, especially induced by carbamazepine, was considered (8). The pathogenesis remains essentially unknown, but recent studies suggest a major role for keratinocyte Fas ligand (CD 95L) in the apoptosis observed in TEN (9). Based on these findings, high dose

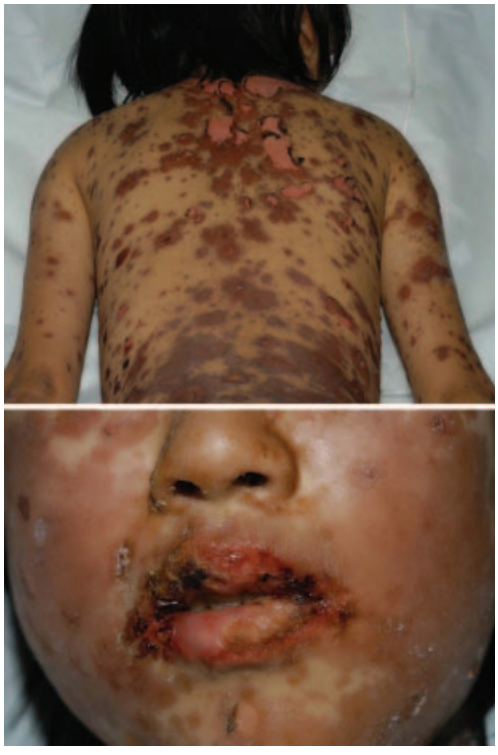

Fig. 1. Toxic epidermal necrolysis in a 12-year-old girl with skin and mucous involvement.

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intravenous immunoglobulin (IVIG) has been regarded as having an anti-Fas activity and has been widely used as a treatment for TEN.

Recently, SCORTEN, a severity-of-illness score for TEN, has been proved to be an accurate predictor of mortality in patients with TEN in Europe and the USA (10). In addition, SCORTEN has been expected to be a predictor of effectiveness in various treatment modalities for TEN.

We carried out a retrospective study of all hospitalized cases of TEN treated at the Asan Medical Center in Seoul, Korea, between 1990 and 2003. Our aim was to determine the aetiology, clinical course, sequelae and role of various treatment modalities in the management and prognosis of TEN using SCORTEN in Korean patients.

PATIENTS AND METHODS

All hospitalized patients diagnosed with TEN between November 1990 and October 2003 were included in this study. Patients were considered to have TEN when they fulfilled the following inclusion criteria: (i) confluence of cutaneous lesions leading to detachment from $>30\%$ of the body surface area (BSA); (ii) mucosal membrane involvement; (iii) histopathological examination of lesional skin showing full-thickness epidermal necrosis.

The search for the drug responsible for TEN was evaluated based on commencement of each individual drug 1–3 weeks before the skin lesion and withdrawal of a drug <1 week before the onset with the exception of those with a long half-life, such as phenytoin. History of current infections or systemic diseases including malignancy was also evaluated. Clinical parameters recorded for each patient included sex, age, indication for drug therapy, extent of necrolysis, body temperature, time from exposure to onset, time from onset to complete healing (or death), delay of hospitalization, associated symptoms and treatment.

SCORTEN was calculated on the basis of seven clinical variables evaluated during the first 24 h of admission: age above 40 years, presence of malignancy, tachycardia above 120/min, involvement of $>10\%$ of body surface area, serum urea >10 mmol/l (28 mg/dl), serum glucose >14 mmol/l (252 mg/dl) and bicarbonate <20 mmol/l (20 mEq/l). This score was calculated by giving 1 point for each of seven clinical values. Patients with 0 to 1 risk factors had an expected mortality rate of 3.2%; 2 risk factors, 12.1%; 3 risk factors, 35.3%; 4 risk factors, 58.3%; and 5 or more risk factors, 90%. The expected number of deaths was calculated for each subgroup. The standardized mortality ratio analysis (SMR) ($[\Sigma$observed deaths/Σexpected deaths$]\times 100$) was then used. The actual mortality rate was compared with the predicted rate. We also used the SCORTEN to evaluate the efficacy of corticosteroids and IVIG therapy.

RESULTS

The 38 patients with TEN consisted of 20 males and 18 females, with a mean age of 44.8 years (range 2–80 years) and a mean $\pm$ SD percentage of BSA involved of $48.7\pm17.1\%$ (range 30–70%).

Cause

Association with a drug was established in 35/38 patients (92.1%) (Table I). Forty-nine drugs from 35 patients were recorded (1.4 drugs per person). The drug classes most commonly involved were antibiotics in 18 patients (47.4%), non-steroidal anti-inflammatory drugs (NSAIDs) in 9 patients (23.7%), acetaminophen and herbal remedies in 5 patients (13.2%) each, corticosteroid in 4 patients (11.4%), phenytoin and chlormezanone in 3 patients (7.9%) each, and amitriptyline and mitomycin-C in 1 patient (2.6%) each. In one case, TEN was associated with an unknown drug used to treat an upper respiratory infection. The current infectious history was established in 14/38 patients (36.8%) (Table I). Among these, upper respiratory infection was identified in 10 patients (71.4%), pneumonia in 3 patients (21.4%) and herpes simplex infection in 1 patient (7.1%). All of these patients also had a history of medication for infection. All the patients showed negativity for the HIV test. Underlying malignancies or meningiomas were present in nine patients (23.7%), while additional patients had other systemic diseases, including pneumonia, arthritis, chronic alcoholism or ischaemic heart disease. We were unable to determine the cause of three other cases, but two of these patients had been involved in gold plating work for 3 months prior to diagnosis.

Clinical course

The mean time from initial drug administration to onset of TEN was 9.8 ± 5.7 days. All except four cases began with fever, sore throat and mucous membrane lesions. A burning or painful rash started on the trunk and face. All patients had lesions in oral mucous membranes, 19

Table I. *Incriminated agents/conditions in 38 patients with TEN*

Agents/conditions	No. of cases/deaths*
Antibiotics[a]	18/5
NSAIDs[b]	9/1
Acetaminophen	5/2
Herbal remedies	5/0
Corticosteroids	4/0
Antiphenytoin	3/0
Other drugs[c]	6/1
Infections[d]	14/3

* Due to multi-drug treatment and complex aetiologies, some patients appear two or three times.

[a]Includes augmentin (3 cases), amikacin (2), ceftriazone (2), trimethoprim-sulfomethoxazole (2), amoxicillin (1), ampicillin (1), cefadroxil (1), ceftazidime (1), cefuroxime (1), norfloxacin (1), ofloxacin (1), tobramycin (1) and vancomycin (1). [b]Includes diclofenac sodium (4 cases), naproxen (2), ibuprofen (2) and mefenamic acid (1). [c]Includes chlormezanone (3 cases), amitriptyline (1), mitomycin-C (1) and unclassified drug (1). [d]Includes upper respiratory infection (10 cases), pneumonia (3) and herpes simplex infection (1).

(50.0%) had ocular involvement and 15 (39.5%) had genital involvement. Thirteen patients (34.2%) had lesions at all three mucosal areas. In addition, one patient with severe nasal mucosal involvement was observed.

We found that the spread of the cutaneous lesions was variable in both extent and time course. The mean time of maximum extension from onset was 4.0 ± 1.9 days. In the absence of infection, new epithelialization appeared within a few days. In places that experience pressure or maceration, including the back, buttocks, axilla and groin, cutaneous healing was delayed. The mean time to skin healing for the 29 survivors was 23.2 ± 6.6 days. Overt associated intestinal symptoms, such as severe abdominal pain and/or diarrhoea, were observed in nine patients (23.7%). Twenty-one patients (55.3%) received corticosteroid therapy, given initially as intravenous methylprednisolone (250–1000 mg/day) and later changed to oral prednisolone. Fifteen of these 21 patients (71.4%) survived. High-dose IVIG (1.6–2.0 g/kg) was administered to 14 patients (36.8%), of whom 13 (92.8%) survived. Adverse effects of IVIG, including headache, myalgia, nausea, transient neutropenia and Coombs positive haemolytic anaemia, were observed in five patients, but these conditions normalized after cessation of IVIG therapy.

Of the 38 patients in our series, nine (23.7%) died. In these patients, the mean time from onset to death was 13.8 ± 6.2 days. Sepsis was highly suspicious in seven of these patients. Other probable causes of death were adult respiratory distress syndrome, pulmonary embolism and oesophageal varix bleeding due to hepatocellular carcinoma. All 29 surviving patients experienced sequelae in the form of pigmentary alteration. In 28 cases, the areas involved showed hyperpigmentation, whereas one showed hypopigmentation. These pigmentary changes usually improved over a period of years. Nail changes, including onycholysis and onychodystrophy, were observed in 18 patients (62.0%), but returned to near-normal within several months after skin healing. Milia occurred in 12 patients (41.4%). Persistent ocular lesions developed in 11 patients (37.9%), 9 of whom had a sicca syndrome and suffered from a 'sandy sensation', whereas the other 2 experienced corneal erosion leading to severe impairment. One of the latter patients received partial corneal graft. Persistent dysphagia due to oesophageal stricture was observed in one patient (3.4%). One patient, who experienced severe nasal mucosal involvement, later developed nasal septal synechiae requiring septoturbinoplasty.

SCORTEN

Based on SCORTEN, the expected mortality rate was 9.699/38 (25.5%). The actual mortality rate was 9 (23.7%) (Table II). With the use of SMR analysis, our actual mortality was not statistically different from predicted risk (SMR = 0.928; 95% CI, 0.424–1.761). In addition, the SCORTEN predicted 5.972/21 deaths (28.4%) in the patients treated with corticosteroids. The actual deaths were 6 (28.6%) (Table II). This SMR analysis demonstrates no significant reduction in mortality for patients treated with corticosteroids (SMR = 1.004; 95% CI, 0.369–2.187). Also using the SCORTEN, the expected mortality was 2.353/15 (16.8%) in the patients treated with IVIG, while one death (7.1%) actually occurred (Table II). The figures, however, were too small to allow any final conclusions about the positive effects of IVIG.

DISCUSSION

TEN is a rare but life-threatening disorder, with an incidence estimated at 0.4–1.3 cases per million person-years (11–14). The disorder seems to be more common among patients with human immunodeficiency virus-1 (HIV-1) infection (15), systemic lupus erythematosus (16), bone marrow transplant recipients (17) and internal malignancy (18), than among non-affected patients.

In our series, underlying malignancies or meningiomas were present in nine patients (23.7%), while additional patients had other systemic diseases, including pneumonia, arthritis, chronic alcoholism or ischaemic heart disease. Severe systemic disease may play a role as a significant risk factor for death in patients with TEN (18). Both intensive therapy of the underlying systemic disease and appropriate treatment for TEN were therefore necessary to improve the survival rate. In addition, a genetic factor is also suggested as a possible cause of TEN. In a recent study, Chung et al. (8) showed that there was a strong association between a genetic marker, the human leukocyte antigen, HLA-B* 1502, and Stevens-Johnson syndrome/TEN induced by carbamazepine in Han Chinese. They suggested that genetic factors influencing drug metabolism and the immune response, including HLA genotype, might be involved in pathogenesis of TEN (8). TEN is usually drug-related (3, 7), with more than 100 drugs implicated as causes of Stevens-Johnson syndrome or TEN (6, 7, 12, 13). In a large international case-control study (7), the risks for these conditions were increased for patients using sulfonamide antibiotics, chlormezanone, aminopenicillins, quinolones, cephalosporins, carbamazepine, phenobarbital, phenytoin, valproic acid, oxicam, NSAIDs, allopurinol, acetaminophen and corticosteroids. The list of culprit drugs may change over time as well as geographically. Some reports indicated that TEN caused by drugs with a long half-life are more likely to induce this reaction and also result in a more fatal outcome (19, 20). In addition, the concomitant use of multiple drugs could be a relative risk factor for development of TEN (21).

Table II. *Comparison of SCORTEN-predicted mortality and actual mortality*

		Predicted mortality		Actual mortality
SCORTEN score	Patients, *n*	%	No. of deaths	*n* (%)
All patients				
0–1	7	3.2	0.224	0 (0)
2	16	12.1	1.936	1 (6.3)
3	8	35.3	2.824	2 (25)
4	5	58.3	2.915	4 (80)
⩾5	2	90	1.8	2 (100)
Total	38	25.5	9.699	9 (23.7)
Corticosteroid therapy				
0–1	4	3.2	0.128	0 (0)
2	7	12.1	0.847	0 (0)
3	5	35.3	1.765	2 (40)
4	4	58.3	2.332	3 (75)
⩾5	1	90	0.9	1 (100)
Total	21	28.4	5.972	6 (28.6)
IVIG therapy				
0–1	3	3.2	0.096	0 (0)
2	8	12.1	0.968	0 (0)
3	2	35.3	0.706	0 (0)
4	1	58.3	0.583	1 (100)
⩾5	0	90	0	0 (0)
Total	14	16.8	2.353	1 (7.1)

IVIG, intravenous immunoglobulin.

In our series, we found that antibiotics were most frequently associated with TEN, followed by NSAIDs. We also found that acetaminophen was associated with TEN in five patients. While not a significant risk factor in France, acetaminophen was a significant risk factor in other countries, a difference that may be due to its rates and purposes of use (7). In five of our patients, TEN was believed to be caused by a traditional herbal remedy. These remedies are frequently used among Asian populations, and similar results were observed in Singapore (22). In Korea, especially, herbal remedies have frequently been used in the general population for various internal diseases.

Factors other than drugs may play a much less prominent role in the pathogenesis of TEN, including infection. In a previous study, several viral infections were reported to be associated with TEN, such as Epstein–Barr virus, cytomegalovirus, human herpes virus-6 and HIV (18). Whether virus itself has a pathogenic role or whether there is simply a non-specific activation of a ubiquitous virus secondary to T-cell activation in response to reactive drug metabolites remains to be determined. However, it has been suggested that underlying viral infections may trigger and activate the severe cutaneous reactions in susceptible individuals receiving drugs.

SCORTEN was first used by Bastuji-Garin et al. (10) to predict the mortality rate of TEN patients. They found that the risk of death of TEN patients can be accurately predicted by SCORTEN based on the seven most important prognostic factors: age above 40 years, malignancy, tachycardia above 120/min, initial percentage of epidermal detachment $>10\%$, serum urea $>$ 10 mmol/l, serum glucose >14 mmol/l and bicarbonate <20 mmol/l. Our study supports the SCORTEN's ability to predict mortality rate in Korean patients with TEN. On the basis of SCORTEN, our expected mortality was 9.699/38 patients (25.5%), not different from the actual mortality, i.e. 9 patients (23.7%) (SMR $=0.928$; 95% CI, 0.424–1.761). To date, several reports regarding the ability of SCORTEN to predict mortality of patients with TEN have been demonstrated in Europe and the USA (10, 23).

There is no specific treatment for TEN. Although some studies have suggested that systemic corticosteroids are mandatory and life-saving (24, 25), other studies did not recommend the use of these agents (26, 27). As TEN is thought to be an immunologically mediated process (9), a short course of high dose systemic corticosteroids (e.g. 350–1000 mg methylprednisolone per day) in the early phase of the disease would be expected to halt disease progression and improve survival. In a large case-control study (7), however, corticosteroid use appeared to be an important risk factor for TEN. These findings suggest that a careful drug history and drug analysis should be performed

prior to starting any treatment, especially as systemic corticosteroid therapy may increase the risk of infection, delay healing, mask early signs of sepsis and induce severe gastrointestinal bleeding (4).

Recently, there have been many reports describing the successful treatment of TEN with IVIG (28–32). IVIG has been found to inhibit Fas-mediated cell death by blocking the Fas receptor (9). In a pilot study, the progression of skin disease in 10 patients with TEN was rapidly interrupted after infusion of IVIG at doses ranging from 0.2 to 0.75 g/kg per day, for 4 consecutive days (9). This was accompanied by rapid skin healing and a favourable vital outcome without significant adverse effects. On the other hand, a recent study does not support the routine use of IVIG treatment for patients with TEN, especially in cases of impaired renal function (33). We had traditionally used corticosteroids as a first-line therapy until IVIG was widely used in the treatment of TEN. In this study, we compared the predicted mortality rate with the observed rate in each patient treated with corticosteroids and IVIG based on the SCORTEN. Treatment with IVIG showed a trend to lower actual mortality than the predicted rate (SMR=0.425; 95% CI, 0.011–2.368), whereas corticosteroid therapy showed no such difference (SMR= 1.004; 95% CI, 0.369–2.187). These results, however, were based on too small numbers to allow any final conclusions to be drawn about the positive effects of IVIG. Further large randomized, placebo-controlled trials are needed to assess the benefits and risks of treating TEN using IVIG.

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