KLİNİK ÇALIŞMA / CLINICAL RESEARCH

BÖLGE YANIK MERKEZİ YOĞUN BAKIM ÜNİTESİ'NDE TOKSİK EPİDERMAL NEKROLİZİS'Lİ HASTALAR

PATIENTS WITH TOXIC EPIDERMAL NECROLYSIS IN INTENSIVE CARE UNIT OF REGIONAL BURN CENTER

Tamer KUZUCUOĞLU[1], Ayten SARACOĞLU[2], Sezer YAKUPOĞLU[1], Tuncay ERHAN[3], Burak ERSOY[4], Recep DEMİRHAN[5]

[1]Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, İstanbul
[2]Bilim Üniversitesi, Tıp Fakültesi, Florence Nightingale Hastanesi, İstanbul
[3]Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi, Genel Cerrahi Kliniği, İstanbul
[4]Maltepe Üniversitesi, Plastik ve Rekonstrüktif Cerrahi Anabilim Dalı, İstanbul
[5]Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi, Göğüs Cerrahisi Kliniği, İstanbul

[1]Clinic of Anesthesiology and Reanimation, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey
[2]Bilim University, Medical Faculty, Florance Nightingale Hospital, İstanbul
[3]Clinic of General Surgery, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey
[4]Department of Plastic, Reconstructive and Aesthetic Surgery, Maltepe University Medical Faculty Istanbul, Turkey
[5]Clinic of Thoracic Surgery, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Turkey

ÖZET

Amaç: *Toksik epidermal nekrolizis (TEN) sepsis ve ölümle sonuçlanan potansiyel hayatı tehdit edici, ender görülen bir hastalıktır. Bu çalışmanın amacı hastanemiz yanık ünitesine kabul edilen 12 TEN hastasına ait mortalite oranı, ilişkili komorbiditeler, klinik ve epidemiyolojik karakteristiklerini belirlemektir.*

Yöntem: *Yanık yoğun bakım ünitesine kabul edilen TEN tanısı konulmuş 12 hasta çalışmaya dahil edildi. Hastaların yaş, cinsiyet, ilaç kullanımı, cilt yanık hasarının derinliği ve yüzdesi, APACHE II skorları, cerrahi girişimler, hastanede kalış süresi, mekanik ventilasyon süresi, komplikasyonlar, mortalite ve morbidite oranları retrospektif olarak dökümante edildi. Hastaların mortalite oranlarının belirlenmesinde Scorten Skalası kullanıldı.*

Bulgular: *Ortalama yaş 35±5,7 yıldı. Erkek hastaların kadınlara oranı 5:7 idi ve ortalama APACHE II skoru 15,4±3,2 idi. Epidermal ayrılma vücut yüzey alanının %75'inden fazla, median hasta yatış süresi 17±1,2 gündü. Bir hastada parasetamol ve etodolak, 3 hastada fenitoin alım öyküsü bulunmaktaydı. TEN semptomları bir başka hastada antitüberküloz tedavisi sonucunda, 4 hastada da sultamisilin tedavisini takiben ortaya çıktı. Diğer hastaların etyolojisi bilinmiyordu. Median mekanik ventilasyon destek süresi 3,2±0,7 gündü. Mortalite oranı %16,6 (2/12) idi.*

Sonuç: *TEN hastaları yüksek mortalite riskinden dolayı değişik yaklaşımlar ve tedavi stratejileri gerektirirler. Sorumlu ilacın erken dönemde belirlenerek kesilmesinin ve bir yanık merkezinde özel destekleyici tedavi ortamının oluşturulmasının toksik epidermal nekroliziste mortalite oranını düşüreceği kanısına varılmıştır.*

ANAHTAR KELİMELER: *Toksik epidermal nekrolizis; erüpsiyonlar; komplikasyonlar; yanık; Lyell sendromu*

SUMMARY

Objective: *Toxic epidermal necrolysis (TEN) is a potentially life-threatening rare disorder, resulting in possible sepsis and death. The aim of this study is to determine the mortality rate, associated comorbidities, the clinical and epidemiological characteristics of 12 TEN patients hospitalized in our burn unit.*

Method: *Twelve patients diagnosed with TEN and admitted to the burn intensive care unit were included in the study. Age, gender, medication, percentage and depth of skin burn damage, APACHE II scores, surgical interventions, hospitalization time, the duration of mechanical ventilation, complications, mortality and morbidity rates of patients were documented in a retrospective manner. The Scorten Scale was utilized to determine the mortality rate of the patients.*

Results: *Mean age was 35±5.7 years. The ratio of males to females was 5:7 and the average APACHE II score was 15.4±3.2. Epidermal detachment was greater than 75% of the body surface area with a mean hospitalization time of 17±1.2 days. One patient had a history of paracetamol and etodolac, 3 had phenytoin medication. TEN symptoms were seen as a result of anti-tuberculosis treatment in another patient and appeared in four patients after treatment with sultamicilin. Other patients had an unknown etiology. Mean duration of mechanical ventilation support was 3.2±0.7 days. The mortality rate was 16.6% (2/12).*

Conclusion: *Due to the high risk of mortality, patients with TEN may require different approaches and management strategies. We concluded that early identification and interception of the responsible drug and the provision of a specialized supportive care in a burn unit may reduce the mortality rate for toxic epidermal necrolysis.*

KEY WORDS: *Toxic epidermal necrolysis; eruptions; complications; burn; Lyell's syndrome*

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Yazışma Adresi (Correspondence):
Dr. Ayten Saraçoğlu, Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi Yanık Merkezi Semsi Denizer Cad. E-5 Karayolu Cevizli Mevkii 34890 Kartal, İstanbul, Türkiye
E-posta (E-mail): anesthesiayten@gmail.com

INTRODUCTION

Toxic epidermal necrosis (TEN) was first described by Alan Lyell in 1956 as a drug related and fatal skin disease (1). TEN develops as a result of wide-spread necrotic damage at the epidermal layer; the apoptosis of the keratinocytes is the principal reason. The drugs or their metabolites are thought to act as haptens initially, binding to the surface of keratinocytes and granting them antigenic properties (2).

The worldwide incidence of TEN is reported to be between 0.4 and 1.3 per 1 million individuals (3). More than 220 drugs were suspected to be related with the TEN etiology. The most commonly accused agents include sulfonamides, antiepileptics, oxicam and nonsteroidal anti-inflammatory drugs, allopurinol, nevirapine, abacavir and lamotrigine. Thiacetazone as an antituberculosis drug was also accused (4). Additionally, infectious agents (mycoplasma pneumoniae, herpes virus, hepatitis A virus), vaccines, bone marrow as well as organ transplantations were also presumed to play a role in the TEN etiology. The differential diagnosis for TEN includes acute generalized exanthematous pustulosis, burn injury, conjunctivitis, cornea ulceration and ulcerative keratodermatitis, exfoliative eosinophilic dermatitis with drug reaction, erythrema multiforme (EMM), phototoxic dermatologic reactions, staphylococcal scalded skin sydrome, Stevens-Johnson Syndrome (SJS) and toxic shock syndrome. The rate of mortality varies between 30% and 50%; currently the Scorten Mortality Score (SMS) is the most frequently utilized method for evaluation of the mortality rate (Table 1, 2). The primary reason of mortality in TEN related deaths were reported to be septicemia and multiple organ failure (5).

The aim of this study is to determine the mortality rate, associated comorbidities, the clinical and epidemiological characteristics of 12 TEN patients hospitalized in our burn intensive care unit.

MATERIALS AND METHODS

Following the approval by the Local Ethics Committee of our hospital, medical records of 12 patients diagnosed with TEN and admitted to our burn intensive care unit between January 2009 and June 2012 were analyzed retrospectively. In all patients blood pressure, heart rate, peripheral oxygen saturation, urine output and body temperature was closely monitored. Following the admission to the intensive care unit APACHE II and mortality scores were calculated for the first 24 hours and the prognosis of each patient was analyzed (Table 1). Necessary medical consultations were carried out and age, gender, previous illnesses and drug history of each patient were recorded. Lund-Bowder scale was utilized to calculate the proportion of the lesions to the total body surface area. Drugs with a suspicious relationship with the TEN etiology were discontinued. All patients received acetylcysteine 300 mg three times a day as an antioxidant, pantoprazol 40 mg three times a day for gastric prophylaxis and also an intravenous administration of a multivitamine complex. As an analgesic agent, tramadol 1-1.5 mg kg^{-1} was administered intravenously three times a day. Following the admission to the intensive care arterial blood gases, complete blood count, biochemical analysis, coagulometry, liver enzymes, C-reactive protein (CRP) and sedimentation rates were routinely monitorized. In patients with a persistent fever above 38°C blood culture analysis was performed. Apart from patients requiring mechanical ventilation no patient received obligatory invasive intervention. Fluid resuscitation of the patients was monitorized with urine output and urine density levels. Ringer's lactate solution was administered intravenously and normovolemia was ensured with a urine output of 0.5 mL kg^{-1} h^{-1}. For the nutrition the caloric need of patients were calculated with the Harris-Benedict formula (30 kcal kg^{-1} day^{-1}) and the patients received Impact Oral RTD (Nestle, Switzerland) five times a day supplemented with two units of Resource Glutamine (Nestle, Switzerland) three times a day orally. Patients with a positive antibiogram result received antibiotic threapy in concordance with the culture results. The patients also received immunotherapy with immunoglobulins 0.5 mg kg^{-1} day^{-1} (IVIG) for three days. The dressings of the patients were renewed every other day and irigation with sterile distilled water was performed under sedation. In TEN patients all data including age, gender, depth of the lesions as well as their ratio to the total body surface area, drugs in usage, comorbidities, the duration of the mechanical ventilation, the duration of stay at the intensive care unit, the complications emerged and the mortality rates were recorded according to the Scorten Mortality Score (SMS) criteria (Table 1, 2).

Table 1: Skorten Mortality Scale (SMS) Criteria

1-Age > 40
2-Heart rate > 120/min
3-Cancer or hematologic malignancy
4-Body surface area involved > 10%
5-Blood Urea Nitrogen > 10 mmol/l (28 mg/dl)
6-Serum bicarbonate level < 20 ml/l (20 meq/l)
7-Blood glucose level > 14 mmol/l (252 mg/dl)

* One point is added for each parameter present.

Table 2. Number of factors present and the corresponding mortality rates

Number of factors	
SMS 0-1	3%
SMS 2	12%
SMS 3	35%
SMS 4	58%
SMS 5 and above	90%

RESULTS

The average age of the patients in the study was 42±3.5 years, ranging between 9 and 64 years of age. Male to female ratio was calculated as 5 to 7. The surface area of the lesions ranged between 75% and 100%. One patient had TEN development following burn injury; for the rest of the patients the lesion depth was noted as superficial (Figure 1).

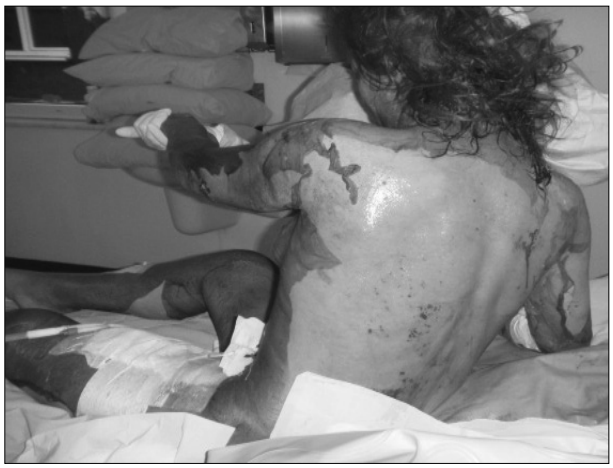

Figure 1: The patient with erythematous and purpuric macula on the skin forming central eruptions on her face and the body

In one patient receiving supportive treatment for Charcot Marie Tooth disease the anamnesis revealed that paracetamol and etodolac was added to the treatment 1 week ago for arthralgia and upper respiratory tract infection. Three of our patients were using phenytoin for the last 4-6 weeks; two of them started it as an anticonvulsant following cranial radiotherapy and the other patient was using phenytoin for its anti-epileptic properties.

One of the patients diagnosed with fever of unknown origin had widespread rash and high fever for the last 3 days prior to the admission to the intensive care unit. Following his admission nonfermentative gram negative bacilli were detected on culture and tygacil at a daily dose of 100 mg was administered in combination with sulperazone at a dose of 2 g three times a day. Upon deterioration of the respiratory functions the patient received mechanical ventilatory support for two days and died of sepsis-related organ failure.

Another patient under mechanical ventilatory support was diagnosed with TEN caused by anti-tuberculosis treatment which was started 2 months ago. On the 20. day of treatment skin rash had developed and following the spread of the rash throughout the body the patient was admitted to the intensive care unit. The patient was intubated and mechanical ventilatory support was initiated but advanced lung dysfunction ensued leading to respiratory failure and death of the patient. One patient stated that he had started sultamicilin at dose of 375 mg twice a day for hoarseness and high fever and skin rash appeared at the 5. day of treatment.

The last patient with mechanichal ventilatory support was a TEN case, which was related to a 2°-3° burn injury (45%) and sultamicilin use at a dose of 1 g three times a day for pseudomonas infection. The patient stayed in the intensive care unit for 33 days. During the stay at the ICU the patient was intensively treated for the burn injury (2 surgical interventions, 15 debridements and irrigations). The patient received hemofiltration treatment for four days in order to remove the burn injury-related preinflammatory cytokines. Upon discharge from the intensive care unit the maculopapullary rash was completely resolved.

In two patients blepharitis and conjunctivitis were detected, which were ocular complications of TEN. Both conditions healed with help of eye drops and ointments. None of the patients exhibited gastrointestinal pathology, bleeding or coagulopathy. The average duration of stay at the intensive care unit was 17±1.2 days (between 7 and 33 days) and the mortality rate of the patients was 16.8%.

Eight patients who did not succumb to disease returned to the ward following the regression of the lesions and the disappearing of the need for intensive care. In 7 days all of them were discharged from the hospital. Only three of the patients required mechanical ventilatory support. In these cases synchronised intermittent mandatory ventilation (SIMV) and pressure support (PS) mode were utilized.

DISCUSSION

It is still a highly debated issue whether TEN constitutes part of the disease spectrum of erythema multiforme (EM). EM exhibits a symmetrical distribution without bullae formation. On the other hand, TEN is a disease which usually appears over erythematous or purpuric macula on the skin forming central eruptions on the face

and the body (6). In TEN the epidermis is detached from the dermis. Diagnostic criteria for TEN includes fever, erosion or bullae formation on over 30% of the total body surface area and the inclusion of the mucous membranes (7). In our study the patients were diagnosed with TEN according to a positive Nikosky sign (superficial detachment of the skin due to trauma and pressure), the combined involvement of the mucous membranes and the skin and the surface area of the lesions exceeding 30% of the total body surface area; skin biopsy for confirmation of the diagnosis was regarded as unnecessary.

TEN is a disease which can be detected in patients of all age groups. TEN following an infection is more frequently observed in children. However the incidence of drug related TEN cases is greater in adult patients. It was previously shown that the age of the patients and the extent of the epithelial involvement were directly correlated with the overall mortality of the patients (8). Compared to the adult patients the average rate of mortality is lower in children. In our study 10 patients were of adult age and two of them succumbed to disease thus our findings are correlating well with other results in the literature. It was also reported that TEN was more frequently observed in male patients (9). In our study the female to male ratio was 7/5.

High fever, cough, sore throat, myalgia, tiredness and influenza-like symptoms are usually the preliminary findings of TEN. Pain over the skin lesions is typically a dominant feature. The mucosa, eyeballs and the genital area are listed as the most frequently involved regions (10). Endorf et al. (11) treated the symptoms of TEN in a nine year old female patient with cortisone for three weeks and reported complete healing. The patient had been on carbamazepine treatment for 10 months and had been receiving phenytoin 4 mg kg-1 day-1 in the last two months when the symptoms of TEN had arised.

We believe that the rapid deterioration of the clinical picture in the patient with a history of anti-tuberculosis therapy was the immune supression under the influence of the disseminated rash of TEN. McGee et al. (12) conducted a study on 199 patients independent from APACHE scores and total body surface area percentages; they reported that 83% of patients with positive culture results who had been referred to the burn centers after the 7. day had passed away whereas only 4% of patients had died who had been referred to the burn centers in the first 7 days. In our study the average duration of time between the initial apperance of TEN symptoms and the admission to the intensive care unit was 4±1.3 days (between 2–6 days). The type of ocular involvement varies between corneal erosions, ulcers and acute conjunctivitis (13). Two of our patients developed blepharitis and conjunctivitis. They received drug therapy under the guidance of ophthalmology department and the lesions significantly regressed after 7 days. Painful genital involvement in addition to the involvement of the respiratory epithelium and other mucosal surfaces including esophagus and colon could be observed in TEN patients. The alteration of the bronchial epithelium can lead to the formation of dyspnea and hypoxemia. However certain laboratory tests can confirm the etiological involvement of a specific drug in this instance.

High risk patients with a score of F3 and above according to the SMS scoring system require admission to burn intensive care units. The provision of their treatment by educated personnel was regarded as necessary for the achievement of an improved patient prognosis (14). In our study all of the patients admitted to the intensive care unit composed of high risk patients with a score of F3 or above.

It was reported that the barrier function of the skin is compromised in severe TEN; in these cases the fluid balance and the pulmonary state of the patients should be closely monitorized in order to minimize the contamination of the lesions and the evaporation from the affected sites (15). The oxygen requirement is normally elevated under hypothermic conditions thus it was recommended to provide an environment with 30–32 °C to the patient in order to prevent hypothermia. In our study the patients were kept in isolated rooms with a thermal regulation system stabilizing the room temperature at 30°C for the prevention of hypothermia occurence. The supportive care constitutes the fundamental feature of the TEN therapy. Patient isolation, fluid and electrolyte balance, nutritive support, pain management and protective wound dressings are among the prominent elements of supportive measures (15). The main targets of the first intervention to the TEN patient include the provision of adequate analgesia, the prevention of secondary infections and the application of the necessary measures to decrease the heat loss and to maintain the fluid and electrolyte balance. The management of pain, a meticulous skin care and an aggressive treatment for fluid and electrolyte balance are of vital importance. It is necessary to provide resuscitation with crystalloids and follow the standard rules defined for burn injuries. The intensive fluid resuscitation usually utilized for serious burn injuries have to be avoided in TEN patients because they typically exhibit a less severe microvascular injury necessitating a less aggressive fluid resuscitation. In TEN patients the provision of an average arterial blo-

od pressure above 65 mm Hg, central venous pressure between 8-12 mm Hg, adequate tissue perfusion and central oxygenation for renal perfusion ($SvC0_2$ > 70%) is regarded as an efficient management (16). There are several studies which documented the recognition of a urine output of 0.5-1 mL kg^{-1} h^{-1} as the physiological threshold (15).

The energy requirements of TEN patients should be very cautiously calculated; especially the hypercatabolism-related increase in loss and energy and proteins may cause a delay in tissue regeneration (17). In our study the level of albumin was kept above 2.5 g dL^{-1} and monitorized daily thus the loss of proteins was compensated. Additionally patients have also received supportive treatment with oral glutamine.

All of the patients were followed up with daily open dressings. If their general conditions allowed, patients were daily introduced to the bath tanks under sedation and debrided with hydromassage and hydrosound methods in sterile distilled water. There is an ongoing debate on whether the wounds of TEN should be debrided or not. Dillon et al. (18) reported that accurate debridment with Versajet was effective in 6 case series. Similarly in our clinic, the standard approach to TEN-related wounds is surgical debridement. Following the debridement procedure patients were dried and especially the transfer of Nicolsky positive cases was undertaken with great precaution. The skin dressings were done with mupirocine 2% cream. Aphtous lesions on the oral and vaginal mucosa were dressed with antiseptic solutions; lesions on the cornea of the eye were dressed with solutions and ointment preparations containing antibiotics.

The prophylaxis with antibiotics is reported to be not indicated in TEN cases as long as sepsis or staphylococcal scalded skin syndrome is not suspected (19). In our study the routine use of antibiotics was avoided except for septic shock patients and TEN patients with a positive culture result.

Plasmapheresis, corticosteroids, cyclophosphamide, cyclosporine, and intravenous immune globulins (IVIG) including TNF-alpha inhibitors are proven to be effective drug alternatives for the standard therapy of TEN (20, 21). Glycocorticoids which inhibit T cell activation and decrease the inflammation is suggested to be utilized in the initial phase of TEN but this recommendation is still a controversial subject. In our study the patient undergoing peritoneal dialysis due to chronic renal failure received prednol 250 mg daily and no side effect was encountered. In our study IVIG was also administered which directly inhibited keratinocyte apoptosis. The clinical course of the patients receiving IVIG treatment was uneventful. We applied IVIG treatment protocol to avoid the risk of systemic infection. Because the IVIG treatment should not be interrupted, we did not use plasmapheresis during the treatment period. On the other hand conventional and double-filtration plasmapheresis are being used increasingly for the treatment of severe toxic epidermal necrolysis (22).

The skin lesions of TEN usually heal in two weeks but the lesions on the mucosal membranes take longer to heal and a characteristic scar generally ensues. Eschar formation may be evident on the infection sites or pressure points. There are several studies which had reported that more than 50% of TEN patients required a prolonged treatment and recovered with a sequelae (23). The studies focused on the genetic susceptibility for TEN revealed that in carbamazepine-related TEN cases a positive correlation existed between HLA-B 1502 and Han Chinese group; thus the Food and Drug Administration in United States recommended watchful utilization of this drug in asian patients who had previously received carbamazepine (24). The other strong connection was the positivity of HLA-B*5801 gene in chinese patients who received allopurinol and developed drug reaction. This correlation between SJS/TEN patients and HLA-B*5801 gene was also documented in various japanese patient groups (25).

CONCLUSION

The first intervention in TEN cases with unknown etiology is the discontinuation of the provocative drug; the patients with a SMS of F3 and above need to be admitted to the intensive burn unit. The cornerstones of the treatment are fluid resuscitation, continuation of the nutritional support and provision of wound management. We believe that the treatment of the cases with a multidisciplinary approach will decrease the mortality ratio.

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