DE GRUYTER OPEN

The Journal of Critical Care Medicine 2017;3(1):29-33

CASE REPORT

DOI: 10.1515/jccm-2017-0002

Toxic Epidermal Necrolysis - A Case Report

Laura Stătescu[1], Magda Constantin[2], Horia Silviu Morariu[3*], Laura Gheucă Solovăstru[1]

[1] Dermatology Department, University of Medicine and Pharmacy "Grigore T. Popa", Iaşi, Romania

[2] Dermatology Department, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

[3] Dermatology Department, University of Medicine and Pharmacy Târgu Mureş, România

Abstract

Toxic epidermal necrolysis (TEN) is an acute, life-threatening muco-cutaneous disease, often induced by drugs. It is characterized by muco-cutaneous erythematous and purpuric lesions, flaccid blisters which erupt, causing large areas of denudation. The condition can involve the genitourinary, pulmonary and, gastrointestinal systems. Because of the associated high mortality rate early diagnosis and treatment are mandatory.

This article presents the case of a sixty-six years old male patient, known to have cirrhosis, chronic kidney failure, and diabetes mellitus. His current treatment included haemodialysis. He was hospitalized as an emergency to the Dermatology Department for erythemato-violaceous, purpuric patches and papules, with acral disposition, associated with rapidly spreading erosions of the oral, nasal and genital mucosa and the emergence of flaccid blisters which erupted quickly leaving large areas of denudation. Based on the clinical examination and laboratory investigations the patient was diagnosed with TEN, secondary to carbamazepine intake for encephalopathic phenomena. The continuous alteration in both kidney and liver function and electrolyte imbalance, required him to be transferred to the intensive care unit. Following pulse therapy with systemic corticosteroids, hydro-electrolytic re-equilibration, topical corticosteroid and antibiotics, there was a favourable resolution of TEN.

The case is of interest due to possible life-threatening cutaneous complications, including sepsis and significant fluid loss, in a patient with associated severe systemic pathology, highlighting the importance of early recognition of TEN, and the role of a multidisciplinary team in providing suitable treatment.

Keywords: dermatological emergencies, toxic epidermal necrolysis, intensive care unit

Received: 18 December 2016 / Accepted: 20 January 2017

Introduction

Toxic epidermal necrolysis (TEN) is still a controversial diagnosis in terms of classification and pathogenic mechanism [1, 2]. Major Erythema Multiforme (MEM), Stevens-Johnson Syndrome (SJS), or Toxic epidermal necrolysis (TEN) are terms that are used as variants of the same disease, although the aetiology and pathogenesis are different. [2] Clinically there are criteria that differentiate the three conditions, the main criterion being the affected body surface area (BSA), linked with the number of involved mucous membranes. According to this classification TEN is the most severe of the three variants, affecting over 10-30% of the BSA. [2]

TEN is one of the major dermatological emergencies, needing rapid diagnosis and treatment in an intensive care unit (ICU) or major burns unit.

The incidence of TEN worldwide is 1-2 cases per million per year. [2] TEN can occur at any age and is more common in women and the elderly. [1, 2]

The drug known to cause adverse cutaneous reactions such as TEN are allopurinol, carbamazepine, lamotrigine, nevirapine, oxicam, NSAIDs, phenobarbital, phenitoin, sulfamethoxazole and other sulfur antibiotics, and sulfasalazine [1-4].

It is a life-threatening condition, which commonly begins with prodromal flu-like symptoms, followed by the appearance of a muco-cutaneous morbilliform rash, initially located at acral areas, but spreading quickly over the body. [2, 3]. Flaccid blisters may occur as the condition progresses, bursting quickly, causing large areas of denudation. The skin is extremely fragile, with denudation or blister formation at pressure sites (Nikolsky sign). Associated with these initial events are the subsequent appearance of muco-cutaneous, ophthalmic, renal, gastrointestinal, lung involvement, major hydro-electrolytic imbalance and sepsis due to supra-infection of the muco-cutaneous lesions. These predispose to death in around 30% of patients. [1, 3]

* Correspondence to: Horia Silviu Morariu: Dermatology Department, University of Medicine and Pharmacy Târgu Mureş, România, Str. Gheorghe Marinescu, Nr. 38, 540139, Târgu Mureş, România, Tel: +40 265 215 551. Email: silviu_morariu@yahoo.com

Survivors are prone to a risk of long term sequelae. The activation of cytotoxic T lymphocytes (CTLs) is the main pathogenic element of the keratinocyte apoptosis and necrosis. [1, 3, 4]

Case Presentation

The present case is of a 66 year-old male patient from a rural area, transferred to the Dermatology Clinic, Emergency Hospital "St. Spiridon" Iassy, Romania, in April 2016 from the Dialysis Center, Hospital Parhon, Iassy, Romania, due to the appearance of a rash, represented by erythemato-violaceous macules and papules, some of them purpuric, isolated or grouped in plaques, located at acral areas and which were intensely itchy. These had occurred within the previous forty-eight hours. Associated with these were post-blister erosions on the oral and nasal mucosa and genital areas with deep fissures, covered by haematic crusts on the lips. The patient complained of accompanying painful burning sensations. Prodromal flu-like symptoms of fever, fatigue, malaise, preceded the onset of skin lesions.

The patient's medical history included a diagnoses of complicated diabetes mellitus type II, treated with insulin, chronic kidney disease Stage 5, chronic haemodialysis, obstructive nephropathy, and right nephrostomy, secondary renal hypertension which had existed for about 30 years, mixed decompensate toxic cirrhosis due to alcohool intake and hepatic encephalopathy, first reported in 2014. The patient was taking insulin 10 UI b.i.d., amlodipine 5 mg q.d. and carbamazepine 100 mg q.d.

Event History

The onset of illness was recorded 48 hours before admission to the Dermatology Clinic, when the patient was hospitalized for haemodialysis in the Nephrology Clinic. The clinical examination revealed a slightly itchy erythemato-papulous rash, on the face, hands, feet accompanied by prodromal flu-like symptoms of fever, fatigue, malaise. The patient's condition was aggravated by the extension of the rash and the appearance of purpuric elements with a tendency to spread. The, appearance of flaccid blisters which quickly erupted, resulted in large areas of denudation.

Given the appearance and progression of the skin lesions a preliminary diagnosis of drug-induced allergic vasculitis was made and the patient was transferred to the Department of Dermatology, to confirm the diagnosis and to establish the therapeutic management.

Clinical examination

Clinical examination at admission revealed malaise, itchy rash with erythemato-violaceous, some purpuric macules and papules, isolated or conflated in patches (Fig. 1,2), disseminated on the trunk, upper and lower limbs and cephalic extremities. Flaccid blisters and erosions, resulting in large areas of denudation, covered over 10% of the skin of the trunk and legs. (Fig. 3) On the oral and nasal mucosa erosions there were deep fissures, some of them covered with haematic crusts. (Fig. 4) On genital mucosa erosions were covered with yellow-white exudates and balano-preputial folding.

The general examination identified high blood pressure (160/120 mmHg), an increased abdominal volume due to ascites fluid, collateral venous circulation on the abdominal wall, without neurological manifestations.

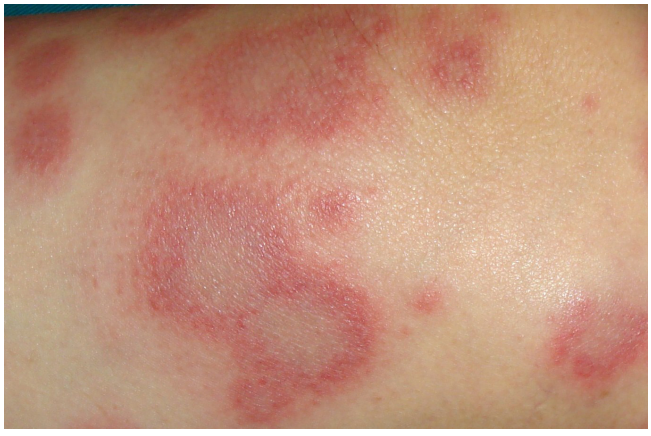

Fig. 1. Erythematous, purpuric macules and papules on the lower limb

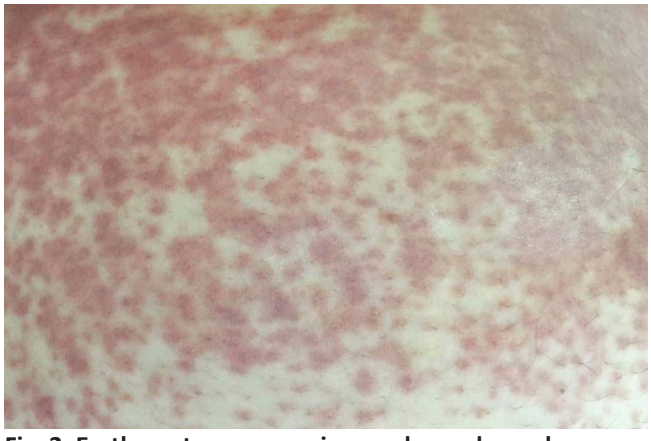

Fig. 2. Erythematous, purpuric macules and papules on the trunk

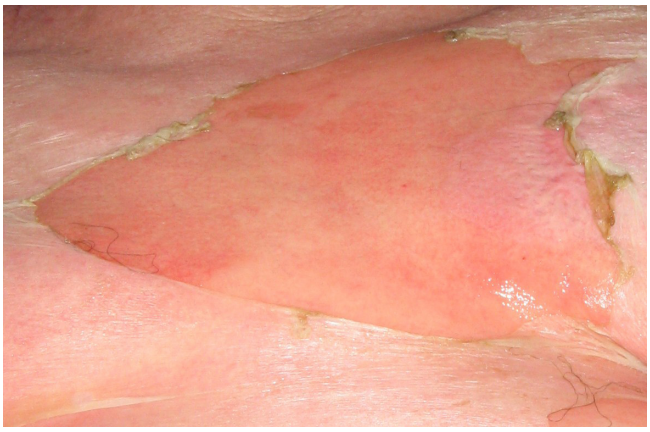

Fig. 3 Extensive denudation on the trunk

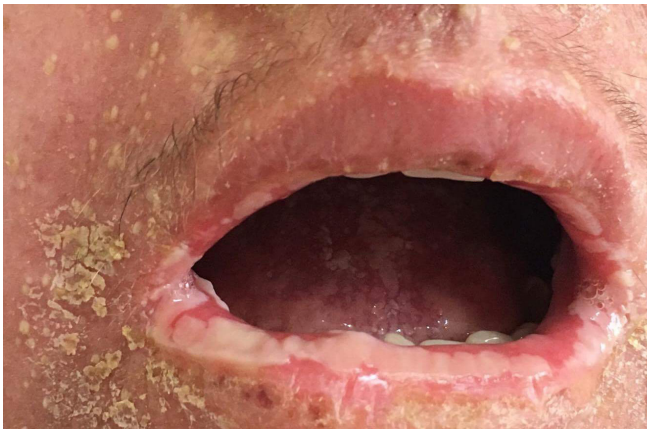

Fig. 4. Erosions on the oral mucosa, erythemato-crustous plaques on the face

Laboratory investigations

At admission to the Dermatology Clinic laboratory investigations revealed marked anemia (RBC 2.22 x 10^6 / µL, Hb 7.6 g / dl, Ht 23.1%), leukocytosis (12.96 x 10^3 / µL) with neutrophilia (10.08 x 10^3 / µL), thrombocytopenia (67 x 10^3 / µL), inflammatory syndrome (ESR 28 mm / 1hr, fibrinogen 593 IU / ml, CRP 3.17 mg / dL), elevated ASLO titer (861 U / ml), elevated IgE (593UI / ml), nitrogen retention syndrome (urea 111 mg / dL, creatinine 4.7 mg / dL, clearance of creatinine 9,7-12 ml/min/1.73 sm, uric acid 9.1 mg / dL) and elevated blood sugar levels (129 mg /ml). Other changes were highlighted hydro-electrolyte imbalance (hypokalemia, low RA), abnormal liver function (GGT 334 U / L), reversing the albumin / globulin rate, and normal values for serum total proteins, INR. A Gram stain and culture from genital secretion and skin lesions, a nasal swab revealed the presence of a bacterial supra-infection with *Klebsiella pneumoniae*, multi-resistant to antibiotics, but sensitive to colistin, amikacin, ertapenem, imipenem, meropenem. The ascites fluid examination revealed numerous red blood and white blood cells, but the absence of pathogens.

Based on the clinical examination and laboratory investigations a diagnosis of toxic epidermal necrolysis was established in a patient with severe kidney disease, vascular decompensated cirrhosis, complicated diabetes mellitus type II.

Considering the general pathology and the patient's systemic medication, a drug reaction syndrome due to carbamazepine was suspected. Given the severity of the muco-cutaneous manifestations the immediate initiation of pulse-therapy with corticosteroid together with topical corticosteroids, topical antiseptics and antibiotics, hydro-electrolyte rebalancing in addition to basic medication for associated pathology was undertaken.

Despite the slightly favorable progress of the skin lesions and the lack of appearance of new elements and a tendency of existing lesions to heal, there was a worsening condition of associated pathologies with high blood sugar values (499 mg / dl) due to systemic corticosteroid administration, worsening of nitrogenous retention (urea 179 mg / dl, creatinine 6.65 g / dL), low alkaline reserve (17.2 mmol / l) with hyponatremia, hypokalemia, associating an episode of upper gastrointestinal hemorrhage, without neurological changes. This resulted in the patient being transferred to an ICU for appropriate treatment.

Treatment in the ICU resulted in the satisfactory resolution of the muco-cutaneous aspects, allowing reduction in corticosteroids after three days with complete discontinuation of systemic corticosteroid after ten days, resulting blood glucose levels returning to normal. Resumption of dialysis and electrolyte rebalancing led to normalization of renal function and acid-basic balance. The patient was discharged from the hospital 15 days after admission to the Dermatology Clinic, with the advice to stop carbamazepine and medically related drugs.

Discussions

Allergic drug induced reactions are one of the most common presentation in an emergency department, but not all of them are life threatening conditions. SJS and TEN are life threatening, usually drug induced severe muco-cutaneous reactions, [1] characterized by blistering and epithelial sloughing. SJS is the less severe and extensive and TEN the most severe and extensive form, and may present with a variety of systemic complications including multi-organ failure. [2].

The key element of the pathogenic mechanism in TEN is the widespread keratinocyte apoptosis. [1] The pathophysiology of TEN is incompletely understood. Current theories connect apoptosis with a Fas-mediated mechanism, a granulysin-mediated apoptosis or the implication of reactive oxygen species. [4, 5] In the immunopathology of TEN, CD8+ T cells act as the major mediator of the keratinocyte death, these cells being found in the inflammatory infiltrate from the superficial dermis and in the liquid of the blisters. [1] Other cells of the immune system (CD4+ cells, CD3-CD56+ NK cells, mast cells, dendritic cells, monocytes, granulocytes and NK/T cells) also involved in the pathogenic mechanism of TEN. [1,3,4] Caproni et al. (2006), reported on a significant presence of CD40 ligand (CD40L) staining cells in the dermis and the epidermis. [6]

CD40L is an important co-stimulator of dendritic cells, B cells, macrophages, epithelial cells, and stimulates the release of proinflammatory tumor necrosis factor-alfa (TNF-α), nitric oxid (NO), interleukin 8 (IL-8), and adhesion molecules. High levels of soluble CD40L (sCD40L) were found in patients' sera, suggesting it as a possible marker for a positive diagnosis in the future. [2,8]

Perforin/granzyme B and granulysin. Granulysin is considered to be linked with the keratinocyte apoptosis in TEN, are implicated in the mechanism of apoptosis in TEN. [1] Chung et al. (2008), found a 10-to 20-fold increased level of granulysin in the blister fluid of patients with TEN. [7] Studies conducted by Abe et al. (2009), found similar changes, suggesting that granulisyn is an inducer of apoptosis in TEN and could also be used as an early diagnostic marker. [8,9]

As there are no markers currently available for the early diagnosis of TEN, the clinical examination of the patient is the most important criteria for a positive diagnosis. Nearly all patients with TEN present major mucosal involvement: painful erosions, ulcerations, inflammation – oral (70-100%), genital (40-63%), ocular (50-78%) involvement [1-4]. Systemic involvement is also described with acute renal failure (5%), adult respiratory distress syndrome, bronchiolitis obliterans (25%), anemia, leukopenia or hepatitis, worsening the prognosis of the disease [1-4]. In our patient associated kidney failure, cirrhosis and diabetis mellitus were agravated by the systemic treatment with corticosteroids and by the fluid loss. Despite all of these systemic complications, infection is the most common cause of death in patients with TEN, and because of this, topical antibiotherapy were administered to the patient in this report .

Bastuji-Garin et al. (2000), developed the SCORTEN score, a recognized and validate measure of disease severity, with the following seven clinical criteria (Table 1).[10].

In our patient the SCORTEN was 4, indicating a high risk of mortality (58,3%) (Table 2) [11].

General management of TEN includes the early withdrawal of any potentially offending drug and the surveillance of the patient in an intensive care unit. Because of the immunological basis of TEN three important drugs are used in the systemic treatment of the acute phase, systemic corticosteroids, intravenous immunoglobulin (IVIg) and cyclosporine. [2-4, 12] Studies regarding the use of IVIg in the terapy of TEN show discordant results. The first meta-analysis conducted by Huang et al. (2012), on the efficacy of IV Ig therapy did not provide sufficient data regarding the proper dose and the benefit of IV Ig in TEN. [2-4, 13] Corticosteroids have been used in the treatment of patients with TEN for a long time, with mixed results, and with an increased risk of associated infections, increased duration of hospital stay, and mortality. Other studies suggest that pulse therapy with corticosteroid (1,5 mg/ kg intravenous methylprednisolone or 100 mg intravenous dexamethasone) for three days is better than a long period of smaller doses of non-pulsed methylprednisolone. [2-4, 14] There is no consensus on the doses or regimen of corticosteroid use in TEN.

Table 1. SCORTEN score: clinical criteria

Risk factor	0	1
Age	< 40 years	> 40 years
Associated malignancy	no	yes
Heart rate (beats/min)	<120	>120
Serum BUN (mg/dL)	<28	>28
Detached or compromised body surface	<10%	>10%
Serum bicarbonate (mEq/L)	>20	<20
Serum glucose (mg/dL)	<252	>252

Table 2. The mortality rate corelated with SCORTEN score

No of risk factors	Mortality rate
0-1	3.2%
2	12.1%
3	35.3%
4	58.3%

Ciclosporine, plasmapheresis, both TNF-α inhibitors, have also been reported but there is no strong recommendation for their use. [2,4]

The presence of characteristic skin lesions made the diagnosis in the current case easier.

Rapid initiation of systemic corticosteroid stopped the development of skin lesions, but upset kidney function and carbohydrate metabolism. Continued haemodialysis, electrolyte rebalancing, and decreasing corticosteroid doses led to the restoration of renal and liver function values, and blood glucose levels.

Conclusion

TEN is a rare but extremely severe, life threatening, drug induced muco-cutaneous disease, which needs to be recognized and immediately treated in special care units. The cessation of the causative drug is the most important step in the treatment of the disease. The patients need to be treated by a multidisciplinary team in an ICU or severe burns unit.

Conflict of interest

Nothing to declare

Refferences

1. Creamer D, Walsh SA, Dziewulski P et al. U.K. Guidelines for the Management of Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis in Adults 2016. Br J Dermatol 2016; 174(6):1194-1227.
2. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necolysis. Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol 2013; 69:173.e1-13.
3. Sassolas B, Haddad C, Mockenhaupt M et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case– control analysis. Clin Pharmacol Ther 2010; 88:60–8.
4. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents – a 6 year series from Chandigarh. India J Postgrad Med 2001; 47:95–9.
5. Viard-Leveugle I, Gaide O, Jankovic D et al. TNFα and IFNγ are potential inducers of Fasmediated keratinocyte apoptosis through activation of inducible nitric oxide synthase in toxic epidermal necrolysis. J Invest Dermatol 2013; 133:489–98.
6. Caproni M, Antiga E, Parodi A et al. Elevated circulating CD40 ligand in patients with erythema multiforme and Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. Br J Dermatol 2006;154:1006-7.
7. Chung WH, Hung SI, Yang JY et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med 2008;14:1343-50.
8. Abe R, Yoshioka N, Murata J, Fujita Y, Shimizu H. Granulysin as a marker for early diagnosis of the Stevens-Johnson syndrome. Ann Intern Med 2009;151:514-5.
9. Abe R. Toxic epidermal necrolysis and Stevens-Johnson syndrome: soluble Fas ligand involvement in the pathomechanisms of the diseases. J Dermatol Sci 2008;52:151-9.
10. Bastuji-Garin S, Fouchard N, Bertocchi M et al. SCORTEN: a severityofillness score for toxic epidermal necrolysis. J Invest Dermatol 2000; 115:149–53.
11. Mahar PD, Wasiak J, Hii B et al. A systematic review of the management and outcome of toxic epidermal necrolysis treated in burns centres. Burns 2014; 40:1245–54.
12. Aihara M, Kano Y, Fujita H et al. Efficacy of additional i.v. immunoglobulin to steroid therapy in StevensJohnson syndrome and toxic epidermal necrolysis. J Dermatol 2015; 42:768–77.
13. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for StevensJohnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol 2007; 87:144–8.