Carbamazepine-induced toxic epidermal necrolysis treated with intravenous immunoglobulin and amniotic membrane: A case report

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Abstract

Introduction: Toxic epidermal necrolysis (TEN) is a distinct clinical entity within a spectrum of adverse cutaneous drug reactions. The common causative drugs are anticonvulsants, non-steroidal anti inflammatory drugs, sulfonamides and other antibiotics. Carbamazepine is an important antiepileptic drug used to treat bipolar disorder, seizures and nerve pain such as trigeminal neuralgia and diabetic neuropathy, which is considered to be one cause of TEN.

Case report
We describe TEN in a 7-year-old Iranian girl with no mucosal involvement treated as an emergency burns case with intravenous Immunoglobulin and amniotic membrane. At the end of the treatment period, there were no scars and good cosmetic results achieved.

Conclusion: We conclude that early diagnosis, supportive care and careful monitoring for complications comprise crucial management in TEN. Moreover, using an effective co-adjuvant treatment (amniotic membrane and intravenous immunoglobulin), will improve the skin lesions of TEN totally without scars.

Key words: Amniotic membrane, toxic epidermal necrolysis, intravenous immunoglobulin

Introduction

Toxic epidermal necrolysis (TEN), known as Lyell's syndrome, lies within the spectrum of severe cutaneous adverse reactions (SCAR) induced by drugs or infections. TEN is an acute life-threatening dermatosis characterized by extensive epidermal sloughing at the dermo-epidermal junction, resulting from hypersensitivity complex and keratinocyte apoptosis (1). This medical emergency presents mucocutaneous tenderness and typically hemorrhagic erosions, erythema and more or less severe epidermal detachment presenting as blisters and areas of denuded skin (affected body surface more than 30% of total body surface area). The incidence is approximately one case per million people per year and the mortality rate varies from 27% to 31% (1, 2). The drugs commonly implicated as the cause of TEN are anticonvulsants, non-steroidal anti-inflammatory drugs, sulfonamides and other antibiotics. Carbamazepine, an important antiepileptic drug, has been reported as having potential to cause serious cutaneous reactions (2). Here, we present a case of TEN occurring 2 days after beginning the use of carbamazepine.

Case Report

On 21 October of 2015, a 7-year-old Iranian girl of Caucasoid origin was admitted to Velayat burn care center in Rasht, a city in north of Iran, with extended skin detachment. 10 days before admission, due to epilepsy disorder, she was treated with Carbamazepine, prescribed by a_ neurologist, starting at curative dosage (150 mg twice daily). Forty-eight hours after beginning the treatment, she presented with fever and developed generalized rash all over her body. Then she was admitted to an internal medicine department. The carbamazepine treatment was stopped and the drug was replaced with Sodium-Valproate. During 7 days, despite treating with topical anti-inflammatory creams and oral non-steroidal anti-inflammatory drugs (NSAIDs), she presented with fever and maculo papular skin eruption extended with few bullae on friction-prone areas and erosions on her oral mucosa and lips. So the doctors made a consultation with a burn fellow and the patient was transferred to this burn care center, 10 days after beginning the use of carbamazepine. On admission, she was suffering from confluent generalized erythema and widespread epidermal necrosis on 54% of her body surface (based on rule of nines: legs (18% ×2 = 36%), the front chest (9%) and the abdomen (9%)) (Figure-1a). Her mental status examination showed total alertness. Also, erythematous papules and vesicles, erosive and crusted lesions, purpuric macules and papules and a flask bulla, with 9x7 cm diameter on the base of the right foot, were presented. She had eroded lesions on the lips covered with hemorrhagic crusts and severe edema of eyelids and lips (Figure-1b).

A positive Nikolsky's sign (denudation of the skin with gentle tangential pressure) was also presented. A bacterial culture test from her skin lesions revealed no growth. She showed no lesions on genital area and conjunctiva. The skin lesions were covered with petrolatum- impregnated gauze. Physical and laboratory data at the first day of admission are shown in Table 1.

Of all SCORTEN (severity-of-illness score) parameters (3), she had 2 positive indexes: Initial surface of epidermal detachment more than 10% and Serum urea more than 10 mmol/l. So she was not managed in the intensive care unit, but transferred to an isolated room and medical treatment with intravenous immunoglobulin (at a dosage of 20 gr daily) and fluid replacement (intravenous dextrose 5%) was initiated. Also, burn wounds were initially cleaned with gentle brushing and using soap and water. Using IVIG for 2 days, 9 day after starting manifestations, her lesions improved with a marked decrease in the flask bulla on the base of the right foot, decreasing body temperature on normal state (no fever), generalized scaling and decreasing in face edema. Figure 2 shows her clinical manifestations after using IVIG.

Due to her situation and because she was not totally cured, we decided to cover the areas of epidermal detachment with two amniotic membranes approved by FDA taken from Iranian Tissue Bank (ITB) which is a multi-tissue bank in Tehran. In the operation room, debridement was performed using gentle mechanical techniques, and then we placed the membrane on her body surface. She was intubated during the whole procedure, and IVIG was maintained. Amniotic membranes dried and were consequently fixed to the skin during the next 4 days. We stopped using IVIG 3_ days after beginning. She improved dramatically during the following 24_ hours after procedure, with a marked decrease in her generalized erythema and swelling (Figure 3).

After time, all erythematous papules and vesicles disappeared and her appetite rose significantly. Complete re-epithelization of the affected skin was observed four days after the membrane placement (Figure 4).

All symptoms and skin lesions resolved progressively. The skin lesions healed without scarring but with hyper-pigmentation (Figure 5). The patient left our department in a good general state on 5 November of 2015.

Figure 1a: the patient's manifestations at the first day of admission.

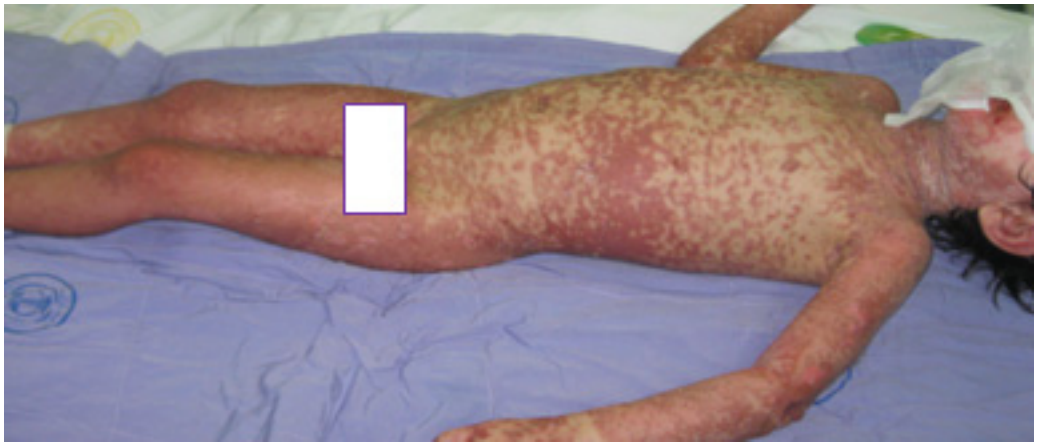


Figure 1b: the patient's manifestations at the first day of admission

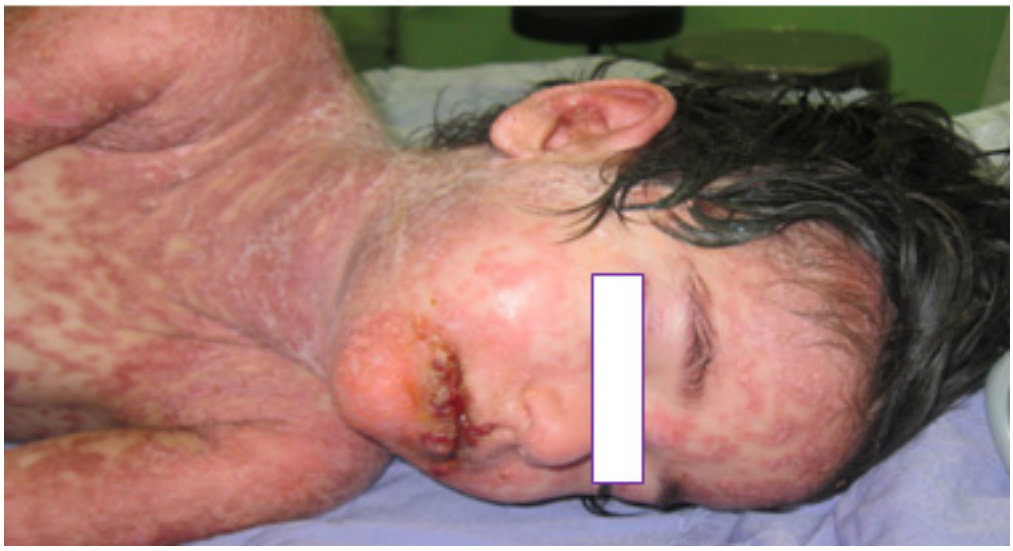


Figure 2: The patient's manifestation improves two days after using IVIG.

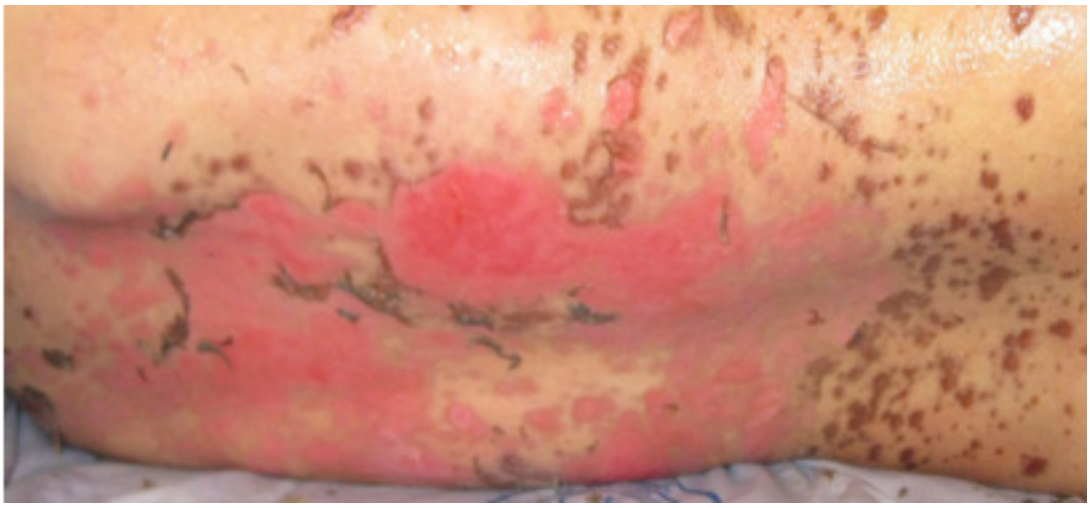


Table 1: Physical and laboratory data of the patient at admission

PATIENT FINDINGS		SCORTEN index
Age (year)	7	(0)
Body surface affected (%)	54%	(1)
Blood pressure (mmHg)	110/70	
Malignancy (history)	No	(0)
Temperature (°C)	38.9	
Pulses/min	78	(0)
Hematocrit (%)	31	
Hemoglobin (g/dl)	11.2	
White blood cell (count/ml)	3.22×10^3	
Platelets/ml	202×10^3	
Glucose (mg/dl)	179	(0)
C-reactive protein (mg/dl)	8.7	
Erythrocyte sedimentation rate (mm/h)	11	
Uric acid (mg/dl)	21	(1)
Creatinine (mg/dl)	0.8	
Sodium (meq/l)	132	
Potassium (meq/l)	4.01	
(meq/l)bicarbonate	19	(0)
Total serum protein (g/dl)	6	
Alanine aminotransferase (u/l)	42	
aspartate aminotransferase (u/l)	41	
Alkaline phosphatase (ng/ml)	121	
	Total SCORTEN: (2)	

Figure 3: The patient's manifestations 24 hours after membrane placement

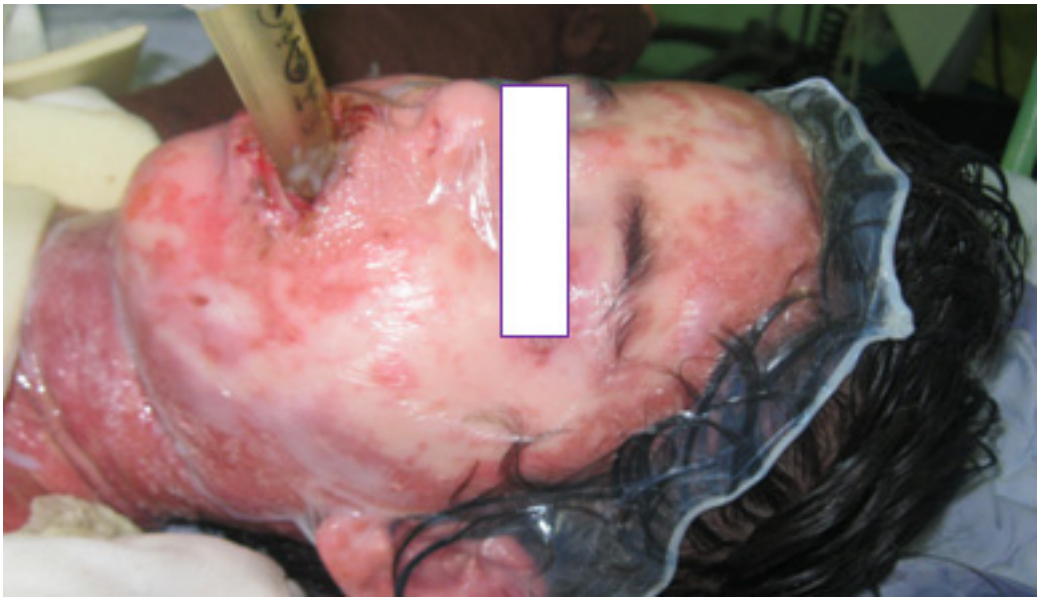


Figure 4: the patient's manifestations 4 days after membrane placement

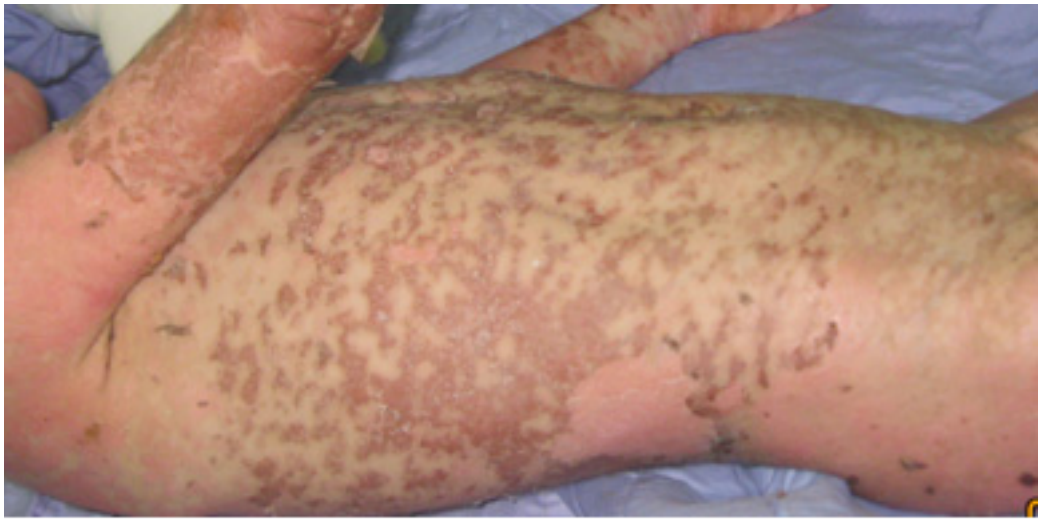
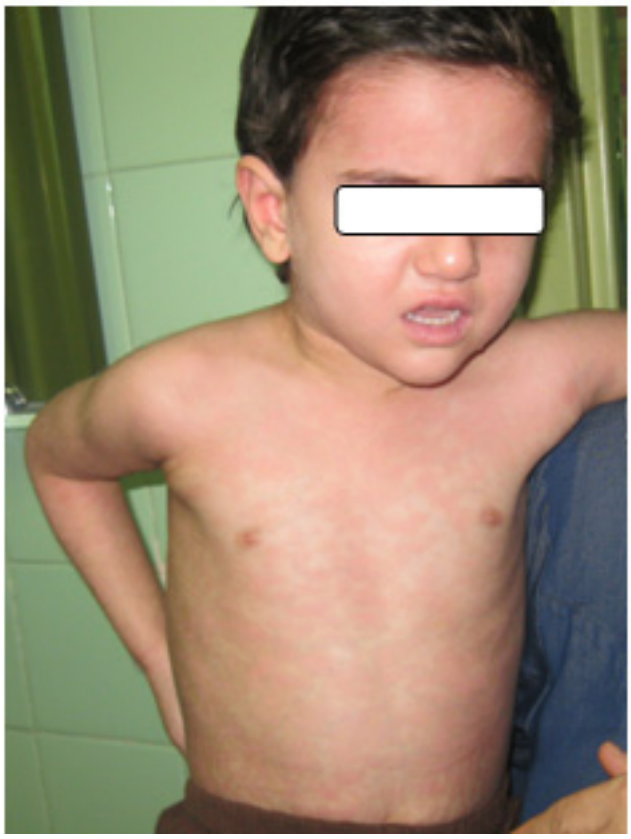


Figure 5: The skin lesions healed without scarring but with hyper- pigmentation



Discussion

TEN is considered as a medical emergency which may be potentially fatal and carries a high mortality rate (2). The disease started with general malaise, myalgia, and prodromal symptoms. A burning, painful eruption spread from the face to the neck and shoulders and later to the entire trunk and proximal parts of limbs. The peak manifestation of lesions usually occurs in a week. In nearly all cases, mucous membranes are involved and Nikolsky's sign is usually positive (3). Different immuno-inflammatory pathways with early participation of activated CD8 T-lymphocytes are involved. Microscopically, there is sub-epidermal bulla formation, with eosinophilic epidermal necrosis. The dermal vessels show endothelial swelling without any vasculitis or necrosis. Ultra-structurally there is damage to the basal and lower spinous levels of the epidermis and cleft formation at the lamina-densa. Immunofluorescences is always negative (1-3).

Drugs are considered to be the commonest cause of TEN. More than 100 different drugs are considered as having caused TEN, but only a minority of them accounts for the majority of cases (2, 3) (Table 2).

Table 2: Drugs that most commonly cause SJS/TEN

Drugs that most commonly cause SJS/TEN	
Antibiotics	Cotrimoxazole/ Sulfonamides, e.g./ Penicillins/ Beta-lactams i.e./ Cephalosporins
Antifungals	Imidazole antifungals
Antivirals	Nevirapine (non-nucleoside reverse-transcriptase inhibitor)
Allopurinol	
Non-steroidal anti-inflammatory drugs (NSAIDs of the Oxicam-type)	Naproxen / Ibuprofen
Anti Convulsants	Carbamazepine/ Phenytoin/ Phenobarbital/ Vaiproic acid/ Lamotrigine

Carbamazepine is used to treat bipolar disorder, seizures and nerve pain such as trigeminal neuralgia and diabetic neuropathy. Some studies showed that among anticonvulsant drugs which induced TEN, the majority of cases were due to Carbamazepine. Also, Konishi et al (4) performed a prospective survey on 335 children treated with carbamazepine and the result showed that the incidence of TEN was 0.6%. So this antiepileptic drug plays an important role in skin reactions and hospitalizations due to these kinds of side effects. Nowadays, according to most authors, systemic corticosteroids are of unproven benefit in the early disease stage and are clearly deleterious in advanced forms of TEN. On the other hand, other investigators consider systemic corticosteroids to provoke prolonged wound healing and increased risk of infection, hiding early signs of sepsis, severe gastrointestinal bleeding and increased mortality (5).

So we did not use systemic corticosteroids for treatment of our patient. Historically, natural amniotic membranes have been successfully used for wound and reconstructive purposes since the early 20th century. Amniotic membrane forms the innermost layer of the placenta which consistos of an epithelial layer and an avascular matrix (6).

There are many reports of using amniotic membrane in treatment of ocular reactions leads to good results. Enhancement of granulation tissue production, production of angiogenic and anti-inflammatory proteins, induction of macrophage apoptosis and a decrease in wound infection rates are advantages in using this method (6-7). In 2002, Dr. John et al (7) presented two patients who were the first cases of acute toxic epidermal necrolysis treated with amniotic membrane transplantation and the first use of the procedure on external eyelid surfaces with good healing of the eyelids. He reported that this new treatment for acute toxic epidermal necrolysis preserves normal ocular and eyelid surfaces and may prevent blindness.

In 2012, Maylon-Hsu et al (8) presented the first case-control study using amniotic membrane in management of 91 cases with Acute Stevens–Johnson Syndrome and TEN ocular lesions. The results showed patients with no acute ocular surface signs (such as our patient in this article) or mild ocular surface inflammation have a good prognosis.

To the best of our knowledge, this is the second case treated with amniotic membrane and IVIG together on skin detachment sites rather than ocular surface on a patient with TEN disorders (9). Today, the effect of amniotic membrane on burnt skin of children is approved (10). But we found no reports of using this method on skin detachment due to TEN in children. So we report this case to present this method as an effective choice to cure TEN detachment lesions on skin. The amniotic membrane plays the rule of an effective barrier to prevent dehydration and infection. On the other hand, we used IVIG which caused a rapid cessation of skin detachment and decreased her temperature.

We believe, despite rare incidence, TEN is a condition with a high level of complications and mortality and it must be considered as an important burn emergency which should be treated in burn emergency units, so that both adequate wound care and essential intensive supportive treatment can be given. Patients with a large degree of affected surface area should be treated as patients with intensive burn injuries, with close monitoring and anticipation that life threatening complications might arise.

We conclude that early diagnosis, supportive care and careful monitoring for complications comprise crucial management in TEN. Moreover, good cosmetic results are an important goal which must be considered during treatment period. Using an effective co-adjuvant treatment (amniotic membranes and IVIG), our patient's lesions improved and her skin was totally without any scars.

Consent:
Written informed consent was obtained from her parents for the publication of this report and accompanying images. A copy of the consent is available in the end of this paper.

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Consent form

Patient Informed Consent:

I ..... hereby consent to allow dr.Mobayen to review my health information for the purpose of presenting my de-identified information at a research conference and to publish as a case report in a scientific journal. I understand that my name will not be associated in any way with the information presented or published. Any information that is obtained that can identify me will remain confidential and will be disclosed only with my permission or as required by law.

If I have any questions about the above, I can contact Dr.Mobayen on this phone number: +989125139506 or this Address (Department of surgery and burn. Velayat Hospital, Parastar Street, Rasht, Iran).

I have read the information. I have been given the opportunity to discuss it. All of my questions have been answered to my satisfaction. This signature on this consent form means that I agree to allow access to my personal health information for the purposes of presentation and publication.

_____ _____ _____/_____/_____

Signature of Patient Name (Printed) Year Month Day*

_____ _____ _____/_____/_____

Signature of Patient's parents Name (Printed) Year Month Day*