CASE REPORT

Oman Medical Journal [2018], Vol. 33, No. 4: 356-359

A Case of Toxic Epidermal Necrolysis Successfully Treated with Low Dose Intravenous Immunoglobulins and Systemic Corticosteroid

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ARTICLE INFO

Article history:
Received: 11 January 2017
Accepted: 2 May 2017

Online:
DOI 10.5001/omj.2018.65

Keywords:
Stevens-Johnson Syndrome; Drug Eruptions; Drug-Related Side Effects and Adverse Reactions; Immunoglobulins, Intravenous.

ABSTRACT

Toxic epidermal necrolysis (TEN), a severe form of Stevens-Johnson syndrome, is an acute life-threatening adverse drug reaction with a mortality rate of approximately 30%. Primary treatment of TEN is usually supportive. The use of intravenous immunoglobulin (IVIG) and corticosteroids are still uncertain, as there are only a limited number of studies comparing the usefulness of these treatments. We report a case of a Filipino male patient who developed TEN, most likely due to one of the medications he received during his course of illness. The patient was admitted to Sultan Qaboos Hospital, Salalah, with fever and diffuse painful maculopapular eruption, which became vesicular and bullous after few days, followed by shedding of large sheets of the epidermis. The patient was admitted initially under medical care, and a diagnosis of TEN was considered later. All unnecessary drugs were discontinued, and the patient was shifted to the burns unit. In addition to standard supportive treatment, a combination therapy of systemic steroid and a low-dose IVIG (1.2 g/kg) divided over three days was administered. This low-dose regimen of IVIG has a pharmacoeconomic benefit compared with the previous cumulative dose (3 g/kg), which is usually given by dermatologists in other institutions to patients with TEN. The outcome was excellent, and the condition recovered almost completely two weeks after starting the treatment without sequelae.

Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is a rare but severe mucocutaneous drug adverse reaction associated with high rate of mortality. Early and prompt detection of this condition, immediate withdrawal of the causative agent,[1] and appropriate treatment plays a vital role in the patient's survival. Drugs are the most common cause of TEN.[2] Widespread epidermal sloughing occurs leaving an exposed dermis resulting in several complications. The mechanism of cell death is apoptosis via drug-induced CD8+ cell exocytosis of granzyme B/perforin and granulysin and through the activation of the Fas-Fas ligand pathway and tumor necrosis factor-alpha/death receptor pathway.[3] For all cases, symptomatic and adequate supportive therapy is crucial, preferably in a burns unit.[4,5] However, the use of specific therapy including systemic corticosteroids or intravenous immunoglobulin (IVIG) is still controversial.[6,7] In some studies, corticosteroids are considered a life-saving therapy if given early during the disease course and in high doses,[8] while other studies have shown that they increase the mortality rate and length of hospital stay.[9,10] Several studies describe favorable outcomes following the use of IVIG[11,12] in contrast to some studies, which reported poorer outcomes.[7,13] However, the cost of IVIG is a major limiting factor.

Here we describe the case of a Filipino male patient with TEN who responded to combination therapy of low-dose IVIG and systemic corticosteroid.

CASE REPORT

A 33-year-old Filipino male, not known to have any medical illnesses, working as a cook on a cruise ship from Dubai to Romania, was referred to Sultan Qaboos Hospital, Salalah, with a history of fever and rash lasting for three days. Fever was intermittent and high-grade and was relieved by analgesics given by the ship staff. The following day, the patient developed a non-itchy rash on his trunk and limbs.

The patient was admitted under the care of the medical team with a provisional diagnosis of dengue

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Figure 1: Denudation of the epidermis in sheets resembling wet cigar paper.

fever. However, the patient's condition did not improve and got worse. Ten days after admission, he was referred to a dermatologist for a second opinion where he was diagnosed with TEN.

On examination, the patient was conscious and uncomfortable. Apart from a fever of 39.8°C and tachycardia of 114 beat/min, his other vital signs were normal. The skin on his trunk and limbs showed extensive blisters and denudation of the epidermis in sheets involving more than 70% of the body surface area [Figure 1]. Skin tenderness and Nickolsky's sign were positive. Bilateral conjunctival hemorrhage and purpuric eruption on lips were evident. Review of systems was unremarkable.

At the time of admission, his biochemical profile was within normal range except for C-reactive protein (CRP) 126.59 mg/L and alanine aminotransferase (ALT) 473 U/L. Later, the wound swab cultures showed *Acinetobacter* and *Pseudomonas*. The blood culture also showed *Acinetobacter*.

On day 10 of admission, the patient was immediately shifted to the burns unit for better supportive care. In addition, adjuvant systemic therapy of 0.1–0.3 mg/kg/day of dexamethasone for two consecutive days, 0.13 mg/kg for first day, and 0.1 mg/kg for the second day combined with 0.4 g/kg/day of IVIG for three days were given.

During the admission period, his condition was complicated by septicemia and disseminated intravascular coagulation, which were managed by broad-spectrum intravenous antibiotics according to culture and sensitivity and supportive treatment (anticoagulants, blood components, and antifibrinolytics).

Despite late initiation of treatment, the time for arresting disease progression and for reepithelialization was significantly short. The patient totally improved within two weeks without any sequelae [Figure 2].

DISCUSSION

TEN is a rare potentially fatal dermatologic disorder, usually caused by a reaction to drugs. The most common cause cited in the literature are sulfonamides, anticonvulsants, allopurinol, non-steroidal anti-inflammatory drugs, and lactam antibiotics (penicillin and cephalosporin).[14] The distinctive feature of TEN is widespread epidermal separation due to keratinocyte apoptosis. Sepsis and multiorgan failure are the main causes of death in such patients.[15]

Apart from discontinuing the drugs that cause TEN,[1] transferring the patient to a burns unit,[4,5] and adequate supportive care, there is no consensus regarding specific TEN management strategies.[16]

Historically, systemic steroid was the first line of treatment for TEN; some studies showed that steroids are associated with increased mortality,[9,10] higher rates of sepsis, and prolonged hospital stay.[9] Nevertheless, mortality from steroid treatment was not detected in a recent retrospective case-control

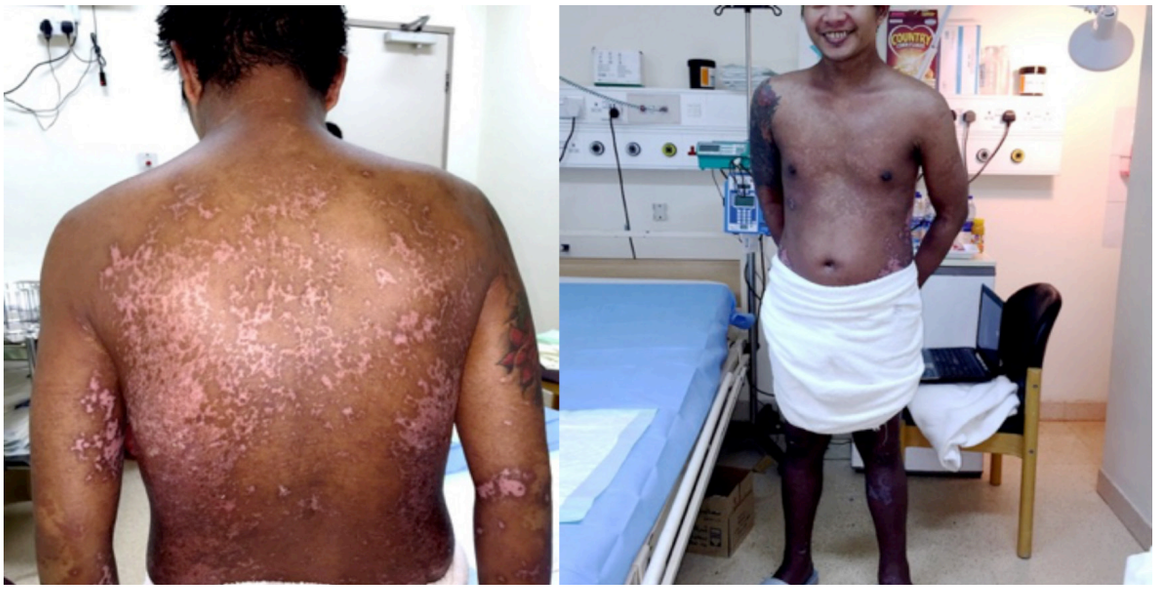

Figure 2: Patient's skin condition on day 14 of treatment, healed totally with depigmented and hyperpigmented patches.

study from Europe.[6] There has been interest in brief high-dose steroid therapy early during the disease course before significant epidermal loss.[8]

On the other hand, IVIG has recently become an important modality of treatment in TEN. Numerous studies describe the favorable outcomes following the use of IVIG.[11,12] However, a meta-analysis including 17 observational studies did not find enough evidence to support IVIG use in patients with TEN.[17] The exact effective dose of IVIG in TEN differs in various studies with most of them employing a total dose of 1.5–3.5 g/kg.[18,19] However, few have reported improvement even with a low dose of 0.1–0.5 g/kg.[20]

In Oman, IVIG has been used in different centers for the management of TEN for the past decade. We use a total dose of 3 g/kg divided over three days and have found it useful in achieving early control of the disease despite many studies claiming otherwise.[21]

Furthermore, the effectiveness of combination therapy of IVIG and systemic steroids was evaluated in several studies. A recent meta-analysis of 26 studies showed that steroid and IVIG combination therapy has an impact in reducing recovery time compared with steroids alone. The favorable effects were greater in Asians and those who received a high dose of IVIG.[22]

The high cost of IVIG makes it difficult to obtain for most patients. Combination therapy with a cumulative low-dose IVIG (< 1.5 g/kg) and steroid is a novel cost-effective therapeutic option for TEN, which has been reported recently in one prospective comparative study conducted to find out the effectiveness of combination therapy of a low dose IVIG (0.2–0.5 g/kg) and rapidly tapering course of steroids (IV dexamethasone 0.1–0.3 mg/kg/day tapered in 1–2 weeks) versus steroid alone.[23] The results supported the use of combination therapy as it was more effective in reducing mortality and accelerating disease resolution. The study hypothesizes that this combination may have a synergistic action targeting the different pathways of apoptosis and preventing disease progression earlier, therefore making the onset of reepithelialization faster and reducing the total steroid dose given earlier.[23] Based on this study, we treated our patient with low-dose IVIG (0.4 g/kg/day for three days) combined with a corticosteroid (dexamethasone for two consecutive days, 0.13 mg/kg/day and then 0.1 mg/kg/day), and achieved excellent results. This case was considered the first in Oman and reported a great result with such treatment.

CONCLUSION

TEN is a rare, life-threatening disorder, generally induced by drugs, characterized by extensive necrolysis, and detachment of the epidermis. Many treatment modalities have been tried; however,

optimal treatment guidelines are still unavailable. Corticosteroids have shown conflicting results, and for high-dose IVIG, the cost is a limiting factor. We achieved an excellent outcome using a new adjuvant treatment for TEN with a combination of low-dose IVIG and a short course of steroids. We suggest that it might be beneficial as well as cost-effective to use this modality of treatment, even in late stages of TEN. Additional randomized controlled trials are needed to confirm this finding. Future research on TEN should focus on adjuvant therapies to establish a standard treatment protocol.

Disclosure

The authors declared no conflicts of interest.

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