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Case Report
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A Different Approach to Toxic Epidermal Necrolysis: Cytokine Filter

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Abstract

Toxic epidermal necrolysis (TEN) is a potentially life-threatening dermatologic disorder that erythema and exfoliation of the skin involve more than 30% of the body surface and usually drug related. A 68-year-old male patient who was admitted to the emergency department with the complaint of extensive bullous lesions on his skin was followed up in the intensive care unit (ICU) with the diagnosis of TEN. He had been on multiple anti-inflammatory, antibiotic and analgesic treatment for approximately 20 days due to respiratory tract infection and gout. Methylprednisolone 1 g day^{-1} was started after the patient's previous treatments were discontinued. The patient was connected to the mechanical ventilator on 11th day due to sepsis and respiratory mucosal involvement. Regression and epithelialisation of skin lesions started after starting cytokine filter treatment on 14th day. The cytokine filter was applied with a renal replacement therapy machine in our patient. Withdrawal of suspected drugs, maintaining an optimal electrolyte balance, sterile care of skin lesions and management in the ICU of specialised centres are essential. Although agents, such as corticosteroids, intravenous immunoglobulins and cyclosporine, are used in the treatment, we think that the use of cytokine filters will contribute to recovery by stopping the cytokine storm in these cases.

Keywords: Cytokine filter, intensive care, toxic epidermal necrolysis, treatment

Introduction

Toxic epidermal necrolysis (TEN) is a potentially life-threatening dermatologic disorder characterised by widespread erythema, necrosis and bullous detachment of epidermis and mucous membranes and can be classified according to its aetiology.[1–3] Erythema and exfoliation of the skin involve more than 30% of the body surface in TEN.

Worldwide, the average annual incidence of TEN is 0.4–1.3 cases per million population.[4] It is believed that TEN is an immune-related cytotoxic reaction that aimed to destroy keratinocytes that express a foreign antigen. The most common aetiology in adults is medication exposure, including antibiotics, antiepileptics, non-steroidal anti-inflammatory drugs, allopurinol, corticosteroids, antiretroviral drugs. However, other aetiologic reasons include infections, vaccinations, organ transplantations, malignancy and idiopathic.

The estimated mortality rate varies between 10 and 70%. Sepsis and multisystem organ failure are the primary causes of death. Epithelial loss results in vulnerability to bacterial and fungal infections. Significant fluid loss from extensive skin exfoliation and an inability to tolerate oral intake can lead to hypovolemia, acute tubular necrosis and shock.

Severity-of-illness score (SCORTEN) that estimates the risk of death in TEN has been developed and validated.[5] Each of the following prognostic factors is given a score of 1: age >40 years, heart rate >120 beats min^{-1}, cancer or haematologic malignancy, involved body surface area >10%, blood urea nitrogen level >10 mmol L^{-1} serum bicarbonate level <20 mmol L^{-1} and blood glucose level >252 mg dL^{-1}.

In this report, we aimed to present the management of an adult patient who was diagnosed with TEN.

Case Presentation

A 68-year-old male patient was admitted to our emergency ward with a complaint of appearance bullous lesions on his skin. He has hypertension, type 2 diabetes mellitus and ischaemic heart disease in his medical history. He

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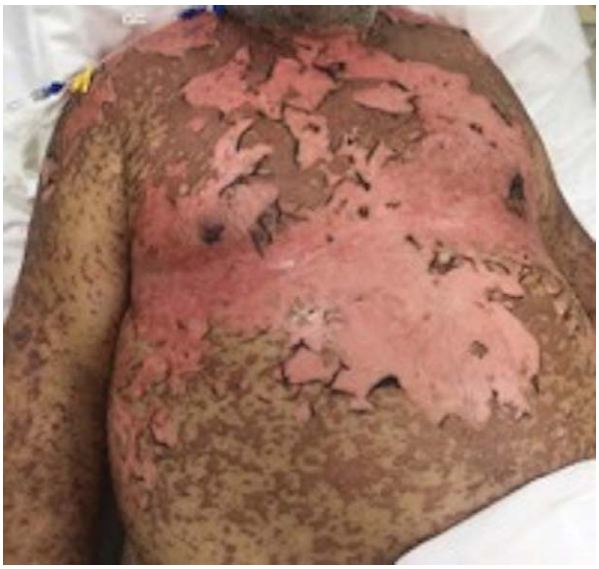

Figure 1. The macular dark-red skin lesions of the patient before treatment.

has been used dexketoprofen trometamol and cefuroxime axetil for upper respiratory tract infection for the last 20 days, thiocolchicoside, diclofenac sodium, and allopurinol for muscle pain and gout disease symptoms for 1 month. Also, clarithromycin treatment was initiated for pneumonia due to high fever 3 days before admission.

The next day, the patient had macular dark red lesions on the abdomen, proximal to the lower extremity, neck, upper extremity and the face (Figure 1). The patient was transferred to the intensive care unit (ICU) from the emergency department with a preliminary diagnosis of TEN. The patient's APACHE-II score was 17, and SOFA (Sequential Organ Failure Assessment) score was 0 at the ICU admission.

On approval, he was conscious, orientated, cooperative. Spontaneous breathing was observed in room air. Respiratory sounds were normal. Dermatology examination revealed diffuse macular red rashes on the skin including, neck, upper extremity and proximal lower extremity. The skin was exfoliated on the anterior and posterior aspects of the body surface, scrotum, lateral aspect of the right neck

Main Points

- TEN is a rare disease with high mortality, often developing against drugs. It progresses with skin rashes.
- Although there is no consensus on its treatment, steroids, IVIG and cyclosporins have been used in the literature.
- In our patient, an acceleration in epithelialisation was observed after the use of cytokine filter, and the effectiveness of the treatment should be investigated by trying in other cases.

Figure 2. The exfoliation on the posterior aspect of body surface.

and most of the back (Figure 2). There were bullous lesions on the chest. Palmar, plantar erythema, erosions in the oropharynx, areas of epidermal integrity were disrupted, erodedried areas of the lips, hyperaemic appearance in the oral mucosa and conjunctiva. The lesions covered more than 40% of the body surface area. The patient's SCORTEN was calculated as four with 58% mortality (age 68, involved body surface area 40%, blood urea nitrogen level 66 mg dL^{-1}, blood glucose level was 317 mg dL^{-1}).

After all previous medications were stopped, intravenous methylprednisolone treatment 1 g day^{-1} for 5 days was started and continued 80 mg twice a day after the fifth day. Electrolyte losses due to more than 40% deterioration of epidermal integrity were replaced with balanced electrolyte solutions. Eroded areas were dressed with isotonic sodium chloride for 10 minutes three times a day. Also, skincare was performed with sterile Vaseline. Epidermal eroded areas progressed to 50% on the fourth day of the ICU. The patient was intubated on the 11th day of hospitalisation due to sepsis with respiratory mucosal involvement and followed up with a mechanical ventilator.

In consultation with infectious diseases, ampicillin-sulbactam was initiated for the first stage of infection control at the admission. The antibiotic treatment was changed to

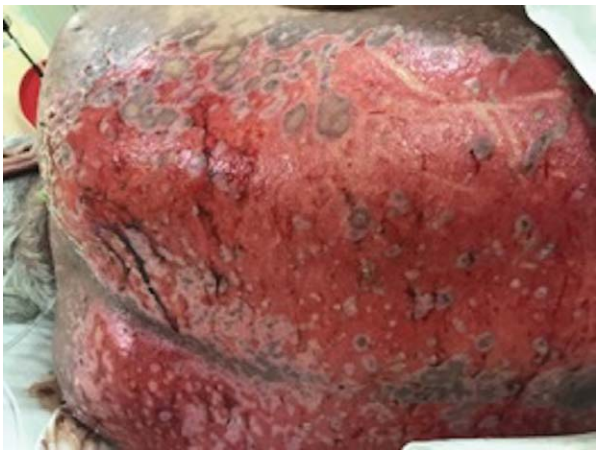

Figure 3. Epithelialisation of the skin lesions after cytokine filter treatment.

piperacillin-tazobactam and ciprofloxacin due to increased CRP and hypothermia. Colistin was started due to *Acinetobacter baumanii* growth in blood culture on the 10th day. Empiric meropenem was added to his antibiotherapy due to increased CRP and procalcitonin. *Meticiline resistant staphylococcus aureus* was growth in catheter culture, and vancomycin was started for treatment on the 11th day. Intravenous phosphomycin and fluconazole were added as a combination therapy because of uncontrolled infection.

Cytokine filter (CytoSorb®, CytoSorbents Corporation, NJ, USA) was applied via continuous veno-venous hemodiafiltration device which was used for acute kidney failure. A cytokine filter was performed on the 14th day and continued for 5 days due to observing no regression in skin lesions and worsened clinical condition. Epithelialisation of the skin lesions was accelerated after this treatment (Figure 3).

Respiratory and hemodynamic parameters of the patient were within normal limits at the time of admission. However, during intensive care hospitalisation, sepsis developed and he received vasopressor treatment for 1 day due to septic shock. Continuous veno-venous hemodiafiltration was performed for 10 days during the follow-up period due to acute kidney injury.

The patient was extubated and mobilised on the 33rd day of hospitalisation. He was followed up in the ICU until the 49th day, and his subsequent follow-up was performed at the plastic surgery service and discharged from the hospital on the 65th day.

Discussion

Early withdrawal of the suspected drugs, maintaining an optimal electrolyte balance, sterile care of skin lesions and management in the ICU of specialised centres are important for TEN treatment. In addition, the proper treatment of sepsis has an important role in reducing mortality.

Therapies for various pathophysiological pathways leading to keratinocyte apoptosis in TEN have been tried in the literature.[4] CytoSorb is a tool that reduces the level of cytokines using sorbent technology and adsorbs the blood cytokines in a concentration-dependent manner. Bottari et al.[6] performed CytoSorb in an 8-year-old patient who was under treatment at ICU due to TEN, and they observed the beneficial effect of CytoSorb on hemodynamic stabilisation. There is no evidence that the cytokine filter has a mortality-reducing effect in sepsis. Also, 2016 surviving sepsis guideline does not make any recommendation about blood purification technologies in sepsis due to the lack of evidence regarding the clinical benefits of these techniques.[7] The cytokine trapping filters for blocking cytokine activation have not been previously performed in adult TEN patients yet. Although the benefit of cytokine filter usage in septic patients has not been clearly observed, in our case we observed significant improvement in the skin lesions of the patient. We thought that the usage of cytokine filter results in avoiding the current cytokine storm, stopping the progression of skin lesions and transition to the healing phase. There is a need for further studies to clarify the effect of cytokine filters on TEN patients.

There are different treatment approaches for TEN. Valeyrie-Allanore et al.[8] evaluated the effect of cyclosporine treatment in SJS (Stevens-Johnson Syndrome) and TEN patients and concluded that cyclosporine reduced the expected mortality according to SCORTEN. Intravenous immunoglobulins (IVIGs) and corticosteroids are other treatment options for systemic therapy.[9] Viard et al.[10] observed that IVIG blocks Fas-mediated necrosis of keratinocytes *in vitro,* and IVIG has been included in the treatment. However, the efficacy of IVIG treatment was evaluated in a meta-analysis and concluded that IVIG did not reduce mortality.[11]. Increased infection rate, delayed epithelialisation and prolonged hospital stay have been reported with steroid use.[12] There is a need for further studies to clarify the potential therapeutic effects of corticosteroids in TEN treatment. In our case, the increased infections and increased length of stay in the ICU may be results from systemic pulse corticosteroid treatment.

Conclusion

Withdrawal of the suspected drug, intensive supportive care and fluid management in specialist centres are very important for the treatment of TEN, and the role of cytokine filter treatment for TEN patients should be evaluated.

Informed Consent: Verbal consent was obtained from the participant who participated in this study.

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