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Plasmapheresis as a treatment alternative in drug-induced toxic epidermal necrolysis – descripttion of three cases and review of the literature

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Abstract

Background. Toxic epiderm al necrolysis (TEN) is a rare, severe autoimmune reaction, most commonly formed as a response to drug treatment. Together with Stevens-Johnson syndrome (SJS), it creates a spectrum of disease, with TEN being more severe. ***Case report.*** We presented a successful treatment of three patients with severe TEN. Due to the rarity of the disease, there is no specific treatment guideline. ***Results.*** In our cases, patients were treated with plasmapheresis with a positive outcome. *Anestezjologia i Ratownictwo 2020; 14: 142-146.*

Keywords: toxic epidermal necrolysis, plasmapheresis, autoimmune diseases, treatment

Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) are rare but life-threatening conditions involving detachment of the skin and mucous membranes. The incidence of TEN is approximately 0.4-1.2 cases / 1,000,000 per year [1,2]. Still, despite the development of treatment modalities, the mortality rate is relatively high and is estimated to be 10-20% of cases [3,4]. The typical manifestation of TEN includes widespread painful blistering and mucosal membrane erosions. TEN is recognized if more than 30% of the skin surface is affected, SJS if less than 10%, and TEN/SJS overlap if 10-30% skin is involved.

A drug-induced immune response mostly causes the initiation of SJS/TEN. This reaction leads to widespread keratinocyte apoptosis, skin sloughing, and blistering. However, not all cases of TEN are associated with medications [5]. Still, 20-30% of patients have an idiopathic or uncertain cause of the syndrome [6]. The most common drugs which initiate TEN include allopurinol, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and anti-epileptic drugs [5].

The prevalence of SJS or TEN after medications has been shown to be closely related to genetic predispositions, which are associated with hypersensitivity reactions [7]. These predispositions result from the presence of alleles known as the "genetic marker." The presence of HLA-B * 1502 was shown to be strongly associated with an increased risk of SJS or TEN after taking carbamazepine [8]. HLA-B * 1511 is also referred to as a risk factor for the syndrome development, whereas HLA-B * 4001, HLA-B * 4601, and HLA-B * 5801 are protective factors in the event of carbamazepine-induced SJS /TEN in the Asian population [9]. Numerous studies have also demonstrated a correlation between the occurrence of HLA-B*5801 and an increased risk of an allopurinol-induced hypersensitivity reaction [10-13].

This study aimed to present three cases of patients

with TEN who were treated in the Intensive Care Unit (ICU) of a university hospital. Moreover, the treatment modalities of TEN syndrome, according to the recent literature, are presented.

Patients and treatment

The patients allowed the authors to present their cases, and their characteristics are shown in Table I. In every case, the syndrome was diagnosed by a dermatologist, and the initial treatment was started in the dermatological department. Only patients in severe conditions, at risk of respiratory distress and the need for plasmapheresis, in the opinion of both dermatologists and intensivists, were transferred to our ICU.

Each patient revealed some common signs and symptoms including

- Painful blistering covering over 50% of the skin surface involving head, torso, and limbs
- Difficult and painful swallowing
- Productive coughing
- A positive Nikolsky sign (dislodgement of the intact superficial epidermis by shearing)

The implemented treatment including

- A series of plasmapheresis
- Steroids
- Clemastin
- Prophylactic antibiotics - doxycycline 100 mg twice a day

In each case, the fresh frozen plasma was used as replacement fluid. The calculated amount of exchanged plasma was 70% for each therapy. Both patients 1 and 2 improved quickly after a series of plasmapheresis – three therapies. Patient 2, due to old age, had plasmapheresis every second day. Because of slower healing, patient 3 had six plasmaphereses, and the additional treatment modalities consisted of cyclosporin, immunoglobulin (Ig-vena), acyclovir, and clindamycin. However, every patient had significant pain relief after plasmapheresis implementation. All patients were successfully discharged from the hospital.

The table presents patients' age in years, sex, a medication which probably induced TEN, the period between the treatment initiation and the first symptoms of TEN. The ICU and hospital stay are presented in days. For each patient, mouth and throat mucosa and ocular involvement are showed as high, most of the area (+), partial (±), and low, none or almost nothing (-). ICU, intensive care unit; TEN, toxic epidermal necrolysis

Discussion

The study presents the successful treatment of drug-induced TEN in the ICU. Although the patients received several medicines during the hospital stay, the significant improvement was noticed after a series of plasmapheresis. Our observation is consistent with previous reports regarding this therapy in patients with TEN [14,15].

The rationale for the usage of plasmapheresis in TEN includes the rapid removal of circulating drugs and antibodies. Although the evidence for the usage of this technique in TEN/SJS appears to be strong, plasmapheresis is not routinely utilized in these patients. The potential reasons for this state comprise lower severity of the syndrome, treatment of patients in dermatological departments, and lack of availability of machines for extracorporeal treatment in hospitals. However, the trend is observed towards the wider usage of plasmapheresis as an initial therapy [14]. Plasmapheresis removes non-dialysis pathogenic elements from the plasma. Additional benefits of plasmapheresis may result from the removal of inflammatory cytokines such as IL6, IL8, TNF-alpha [16].

In three cases presented in our study, plasmapheresis was used in addition to supportive care and glucocorticosteroids. Patient 1 was treated three times on three consecutive days, while patient 2 was performed every two days due to the patient's age and limitation of his body capacity. Plasmapheresis, in the case of TEN is used relatively rarely, and the research

Table I. Patients characteristics

Patient	Medication inducing syndrome	TEN onset	ICU stay (days)	Hospital stay (days)	Mouth and throat mucosa	Ocular involvement
1. 61 y female	Allopurinol	2 months	4	18	+/-	-
2. 90 y male	trimethoprim/sulfamethoxazole	2 week	5	46	-	-
3. 73 y male	Allopurinol	4 weeks	15	30	+	+

examining its effectiveness differ in results [17]. Some available publications do not confirm its effectiveness [18]. At the same time, many studies indicate that the use of plasmapheresis can have good therapeutic effects in patients with TEN/SJS and is a promising treatment method [19-21]. Publications from Japan indicate good efficacy of using plasmapheresis in patients with skin lesions occupying less than 30% of the body surface, and when the therapy is started early. However, proper treatment results in this country may be related to different diagnosis criteria of TEN and specific management algorithms.

In the current study, the first and the third patient had taken allopurinol for weeks before the first symptoms appeared. According to the literature, the first 60 days from the beginning of the treatment are correlated with the highest risk of TEN/SJS development [13]. The second patient was treated with co-trimoxazole, which could have been a trigger for the disease, but the effect of NSAIDs cannot be excluded here.

Due to the fact that TEN/SJS is a rare disease, there is no strict treatment protocol, and the patient's condition should be managed individually. The most common treatment methods include the use of glucocorticoids, cyclosporin A, cyclophosphamide, immunoglobulins (IVIG), anti-TNF, and plasmapheresis.

Numerous studies indicate that the most important element of TEN/SJS therapy is supportive care, consisting of maintaining hemodynamic equilibrium and preventing life-threatening complications, management of airway, renal function, fluid and electrolyte balance, nutrition, skin and ocular surfaces, pain control, and prevention of infection [17,18,22].

Glucocorticosteroids are one of the most commonly used means in SJS-TEN therapy [17]. The effectiveness of treatment depends on the sensitivity of the cell-type allergic reaction to the action of steroids. Early incorporation of glucocorticosteroids into therapy is associated with better treatment outcomes [23]. According to some sources, steroid therapy is associated with a reduction in overall mortality and some complications of the disease, including those related to vision [7,17]. However, the results of the studies are inconclusive, and some reports showed no difference in the effects of treatment between supportive care and the use of steroids [18].

Cyclosporin is the second most commonly used drug in SJS/TEN therapy [24]. Cyclosporin is a calcineurin inhibitor that blocks the activation of T-cell lymphocytes responsible for keratinocyte apoptosis [25]. It reduces mortality and enhances the reepithelialization process, thus shortening hospitalization time and treatment costs [26,27]. A study comparing cyclosporin and glucocorticosteroid treatment was published, and the cyclosporin-treated group stayed in the hospital shorter, achieved faster reepithelialization comparing with the glucocorticosteroid-treated group. In addition, no deaths were reported after cyclosporin treatment [28]. Although the administration of cyclosporin seems effective and safe, it might cause a number of complications, especially for people in immunosuppression and renal failure [25]. In the current study, cyclosporin was added as a supportive medicine in patient 3.

Cyclophosphamide action is probably based on inhibition of CD8 + T cell proliferation, which is associated with apoptosis of keratinocytes in TEN/SJS [29]. In one study, the 300mg dose successively reduced to 100mg/day for 6 days was used with good effect [20].

N-acetylcysteine action is based on increasing the concentration of glutathione, being its precursor. Glutathione scavenges free radicals and inhibits the NF-κB transcription factor. Saavedra (2012) used 600 mg of N-acetylcysteine every 8h for two days and observed a significant improvement in patients with TEN [30].

Many studies indicate good efficacy of IVIG, but their quality is disputable. The use of 1-3 g/kg of body weight for 3-5 days is commonly recommended [31-34]. Morci et al. proved that the use of IVIG was associated with a decrease in fever and a shortening of hospitalization in children. Still, no statistical significance was observed in the conservatively treated control group [35]. Moreover, advanced age and renal failure are contraindications for the use of immunoglobulin therapy [36]. However, in our study, patient 3 received immunoglobulin as well.

Summary

The use of plasmapheresis was the basis for the treatment of the patients described above and brought a positive therapeutic effect. Plasmapheresis is a promising method of treatment for TEN/SJS; however, due to the small number of studies, ambiguous results, and the lack of a specific protocol, clinical situations in which this method would be the best therapeutic option cannot be determined.

Conflict of interest
None

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