Case report / Приказ болесника

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Case report of a patient with toxic epidermal necrolysis with complications and review of literature
Приказ случаја пацијента са токсичном епидермолизом са компликацијама и преглед литературе

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SUMMARY

Introduction Toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome, is rare exfoliative disorder with high mortality rate. This entity was first described by Lyell in 1956, who termed the condition ‘toxic epidermal necrolysis’, pointing out that drug sensitization was generally considered to be the mechanism leading to this syndrome. The drugs most frequently involved are nonsteroidal anti-inflammatory drugs (NSAID), chemotherapeutic agents, antibiotics, and anticonvulsants, although virus, bacterial, and fungal infections, as well as immunization, have been described.

Case outline We present a 72-year-old man with the following history. Five days before he was admitted patient have had high fiver and pain throat. He was treated with antibiotics and nonsteroidal anti-inflammatory drugs (NSAID) because had had bronchopneumonia and after that he developed itchy skin rash over all body following with sensation of slight sore throat with conjunctival hyperaemia and hard breathing and high fiver and because of this he was hospitalized in the local hospital. After worsening of symptomatology following with urticaria like plaques and then bullae with progression all over the body patient was moved to our Institution and positioned in intensive care unit, under suspicion of TEN. The aim of the paper presented here is to give a thorough summary of our literature review searching for the best therapy modalities for our patient with TEN.

Conclusion We decided to present this case because our patient had been affected with lesions of multiorgan system and with affecting 80% TBSA and SCROTEN score 4. With early diagnosed of TEN patient was successfully treated.

Keywords: toxic epidermal necrolysis; drug induced TEN; burn units

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necrolysis’, pointing out that drug sensitization was generally considered to be the mechanism leading to this syndrome. Stevens-Johnson syndrome (SJS) was first described in 1922 by A.M. Stevens and F.C. Johnson in a report of two young boys, as an acute mucocutaneous syndrome with eruptive fever, stomatitis, and ophthalmia [1, 2]. The drugs most frequently involved are nonsteroidal anti-inflammatory drugs (NSAID), chemotherapeutic agents, antibiotics, and anticonvulsants, although virus (Herpes simplex virus), bacterial (Mycoplasma pneumoniae), and fungal infections, as well as immunization, have been described. Well-known drugs that can induce TEN or SJS are: allopurinol, trimethoprim-sulfamethoxazole, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital and NSAID’s. Recent studies suggest that several drugs, such as carbamazepine and allopurinol, are reported to have a strong relationship with a specific human leukocyte antigen (HLA) type. This relationship differs between different ethnicities [3, 4]. TEN and SJS are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by their extent of skin detachment [3].

The incidence of TEN is very low 1-2 per million, but reported mortality rates vary from 20 to 60 percent. Although a study in the USA indicated that the incidence rate is 1.58 to 2.26 cases/million people, the overall incidence of SJS/TEN remains unclear [4,5]. Some study of HIV-positive patients shown much higher incidence rate than other population. Disease severity and prognosis can be further delineated utilizing the SCORTEN criteria [6, 7].

The pathogenesis of TEN is still not fully clear. The widespread epidermal death is thought to be a consequence of keratinocyte apoptosis. The majority of studies focus on the role of T cells. Recent studies indicated that TEN may be an MHC-class-I-restricted specific drug sensitivity resulting in clonal expansion of CD8+ cytotoxic lymphocytes with potential for cytolysis. Dysregulation of tumor necrosis factor (TNFα) system is also likely to be involved in TEN pathogenesis. Functional studies showed that FAs-L was typically active on
keratinocytes in TEN. The expression of Fas-L on human keratinocytes is upregulated by cytokines including IL-1β, IL-15, IFN-ϒ, and TNF-α realized by keratinocytes themselves and also by skin-infiltrating immunocompetent cells [8, 9, 10, 11].

The clinical course of TEN characterized by a prodromal phase with influence-like symptoms followed by intense erythema, urticarial plaques, and bullae with progress over a day or two to a more generalized epidermal slough, with involvement of the mucosal surfaces. Progressive neutropenia and thrombocytopenia may develop within a few day and, together with septic complications, may lead to multiorgan failure and death. The severity-of-illness score for TEN (SCORTEN) is a measure of severity of illness for toxic epidermal necrolysis. A score is determined by the number of risk factors that are present. The higher the score is, the greater the mortality rate for the patient. The presence or absence of seven risk factors is used to determine the SCORTEN: (1) age >40 years, (2) malignancy, (3) total body surface area affected >10 percent, (4) heart rate >120 beats per minute, (5) blood urea nitrogen >28 mg per dl; (6) serum glucose >250 mg per dl; (7) serum bicarbonate <20 mEq per l. The absence of a risk factor is scored as zero; the presence of a risk factor is scored as one. SCORTEN ranges from zero to seven [3].

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CASE REPORT

We present a 72-year-old man from small town who presented with five days of high fever and sore throat and was diagnosed with bronchopneumonia. Patient was treated with antibiotics (Amoxicillin and Gentamicin) and nonsteroidal anti-inflammatory drugs (NSAID). After 5 days he developed itchy skin and rash all over the body followed sore throat, conjunctival hyperemia and difficulty breathing. He was initially hospitalized in the local
hospital. After worsening of symptoms followed by urticaria and bullae with progression all over the body patient was hospitalized at our Institution, in intensive care unit of burn unit, under suspicion of TEN.

In intensive care unit, physical examination revealed 80% TBSA was affected with severe bullous skin changes, following with conjunctival hyperemia, eyelid edema, oral mucosae erosions, edema of the tongue, auricula of the ear and external ear canal with deepithelization of the skin. Severe balanitis was observed too. Patient had difficulty of speaking because oral mucosa lesion, and with 80% TBSA skin affected with severe bullae which gave us a picture of superficial major scald burn that affecting 80% TBSA. The examination of the eyes by an opthalmologist found deepithelization of the borders of the eyelids with corneal epithelium lesion. The patient was examined by otorhinolaryngologist and was found to have ulcerations and erosions in vestibule of the nares, oral cavity and tongue, hyperemia of epiglottis and hypopharynx. Additional laboratory analysis such as T Pallidum, M. Pneumoniae, HIV, HBSAg, anti HCV which all were negative. Chest X ray revealed diffuse opacity, more intensive at the basis of the lungs, which correlated with bronchopneumonia. Laboratory findings were: WBC 10,5; RBC 4,26; HGB 124; HTC 0,370; PLT 340, CRP 130,1, coagulation panel was normal.

The patient had a history of seizures, COPD, GERD. His home medications were: phenobarbital, aminophylline and ranitidine.

We started treatment like a treatment of major burn injury of II a degree with fluid resuscitation according to the modified Burk formula. Patient had positive Nikolsky sign between affected skin lesions. Local treatment included wound debridement and application of Vaseline gauze and boric acid solution, every day wound debridement and bandage, antibiotic therapy with Vancomycin and Cefepime according to sensitivity. Corticosteroids were
excluded because wound healing. We stopped phenobarbital and NSAID as a possible promoting of TEN.

Our patient didn’t require mechanical ventilation. SCROTEN score on day one was 4 and on day three also was 4 and SCROTEN score represented high mortality rate risk. A skin biopsy confirmed the diagnosis of TEN. After intensive treatment we noticed decrease of rash and partial epithelization with skin pilling in the areas which were not involved.

We obtained verbal and signed consent of the patients to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the principles of the Declaration of Helsinki. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All authors read and approved the final manuscript.

DISCUSSION

TEN is an acute, life-threatening, exfoliative disorder with high mortality rate. High clinical suspicion, prompt recognition, and initiation of supportive care are mandatory. Once diagnosed, the management of SJS/TEN focuses primarily on supportive care and wound management with the addition of adjunctive medications. Thorough investigation of the pathogenic mechanisms is fundamental. The definitive management of SJS/TEN remains to be established. Supportive care is the most universally accepted intervention for SJS/TEN.

Granulysin and CCL-27 serum markers are elevated in patients with SJS/TEN and can be helpful markers to monitor disease severity, reported in recent studies [12, 13, 14]. Further research is required before these markers can be reliably used for diagnosis [15, 16].

Recently published study shows possible connection between TEN and positive diagnosis of COVID-19 [17].
Furthermore, even after recovery, sequelae such as blindness remain in some cases [4, 12]. Approximately 50% of SJS/TEN patients diagnosed by dermatologists and/or in burn units suffer from severe ocular complications (SOC) such as severe conjunctivitis with pseudomembrane and ocular surface epithelial defects in the acute stage. In the chronic stage, this results in sequelae such as severe dry eye and visual disturbance [13].

Specific guidelines differ from the care required for patients with thermal burns. The effective use of IVIG for part of the disease spectrum is not well documented. A consensus regarding combined corticosteroids and intravenous immunoglobulin (IVIG) has not been reached. However, optimal therapeutic options such as systemic corticosteroids, intravenous immunoglobulin, cyclosporine, and TNF-α antagonist are still controversial. Recently, the beneficial effects of cyclosporine and TNF-α antagonists have been explored [8, 12].

Further studies to elucidate the pathogenesis of SJS/TEN are needed.

We decided to present this case because our patient had been affected with lesions in multiorgan system with superficial major scald burns that affecting 80% TBSA with successful outcome. While supportive care measures may seem an obvious aspect of SJS/TEN patient care, providers should understand that these interventions are imperative and that they differ from the care recommended for other critically ill or burn patients.

**Conflict of Interests:** None declared.
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Figure 1. Patient photograph on admission
Figure 2. Patient photograph – closer view on patient rash on admission