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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Case report of a patient with toxic epidermal necrolysis with complications and review of literature

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SUMMARY

Introduction Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is a rare exfoliative disorder with a 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 viral, 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, the patient had high fiver and sore throat. He was treated with antibiotics and NSAID because he had bronchopneumonia, after which he developed itchy skin rash all over his body, followed by the sensation of slight sore throat, with conjunctival hyperemia and hard breathing and high fiver, due to which he was hospitalized in the local hospital. After worsening of the symptoms, followed by urticaria-like plaques and bullae with progress all over the body, the patient was moved to our institution and placed in the 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 Our standpoint is that TEN patients with multiorgan system lesions, with 80% of the total body surface area affected, and with SCORTEN scale score of 4 can be successfully treated if diagnosed early.

Keywords: toxic epidermal necrolysis; drug induced TEN; intensive care unit

INTRODUCTION

Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is rare exfoliative, life-threatening disorder, drug-induced, mucocutaneous disease, with high mortality rate. This entity was first described by Lyell [1] 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. Stevens–Johnson syndrome (SJS) was first described in 1922 by Stevens and Johnson [2] in a report of two young boys, as an acute mucocutaneous syndrome with eruptive fever, stomatitis, and ophthalmia. The drugs most frequently involved are nonsteroidal anti-inflammatory drugs (NSAID), chemotherapeutic agents, antibiotics, and anticonvulsants, although viral (herpes simplex virus), bacterial (*Mycoplasma pneumoniae*), and fungal infections, as well as immunization, have also been listed. Well known drugs that can induce TEN or SJS are the following: allopurinol, trimethoprim-sulfamethoxazole, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital, and NSAIDs. Recent studies suggest that several drugs, such as carbamazepine and allopurinol, are reported to have a strong relationship with a specific human leukocyte antigen 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 cases per one million people), but reported mortality rates vary 20–60%. Although a study in the USA indicated that the incidence rate is 1.58–2.26 cases per one million people, the overall incidence of SJS/TEN remains unclear [4, 5]. Some studies of HIV-positive patients show a much higher incidence rate than in other populations. 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 indicate that TEN may be an MHC-class-I-restricted specific drug sensitivity resulting in clonal expansion of CD8+ cytotoxic lymphocytes with a potential for cytolysis. Dysregulation of the 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

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by cytokines including IL-1β, Il-15, IFN-Y, and TNF-α realized by keratinocytes themselves and also by skin-infiltrating immunocompetent cells [8–11].

The clinical course of TEN is characterized by a prodromal phase with influenza-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 days 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. The score is determined by the number of present risk factors. 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%, (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 0–7 [3].

The aim of the paper presented is to give a thorough summary of our literature review searching for the best therapy modalities for our patient with TEN.

Figure 1. Patient photograph on admission

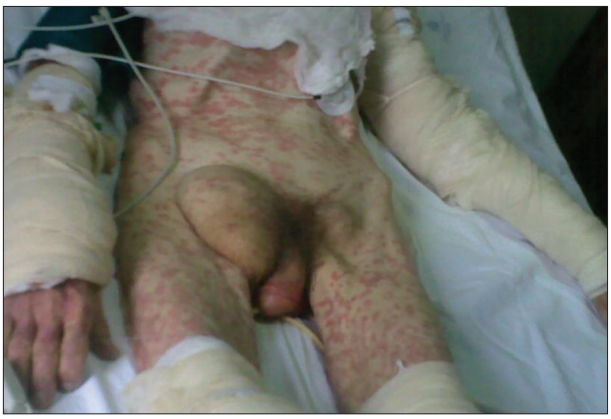

Figure 2. Patient photograph – closer view on the patient's rash on admission

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. The patient was treated with antibiotics (amoxicillin and gentamicin) and NSAID. After five days, the patient developed itchy skin and rash all over his body, followed by sore throat, conjunctival hyperemia, and difficulty in breathing. He was initially hospitalized in the local hospital. After worsening of symptoms followed by urticaria and bullae with progression all over his body, the patient was hospitalized at our institution, in the Intensive Care Unit, under suspicion of TEN.

In the Intensive Care Unit, physical examination revealed 80% of the total body surface area (TBSA) was affected with severe bullous skin changes, followed by conjunctival hyperemia, eyelid edema, oral mucosae erosions, edema of the tongue, auricula of the ear and the external ear canal, with de-epithelization of the skin. Severe balanitis was observed as well. The patient had difficulty speaking due to the oral mucosa lesion, and with 80% of the TBSA affected with severe bullae, which gave us a picture of a superficial major scald burn that affected 80% of the TBSA. The examination of the eyes by an ophthalmologist found de-epithelization of the borders of the eyelids with corneal epithelium lesion. The patient was examined by an otorhinolaryngologist and was found to have ulcerations and erosions in the vestibule of the nares, the oral cavity, and the tongue, hyperemia of the epiglottis and the hypopharynx. Additional laboratory analyses, such as *Treponema pallidum*, *M. Pneumoniae*, HIV, HBSAg, anti HCV, were all negative. Chest X-ray revealed diffuse opacity, more intensive at the basis of the lungs, which correlated with bronchopneumonia. Laboratory findings were as follows: white blood cell count 10.5; red blood cell count 4.26; hemoglobin 124; hematocrit 0.37; platelet count 340; C-reactive protein 130.1; coagulation panel was normal.

The patient had a history of seizures, chronic obstructive pulmonary disease, gastroesophageal reflux disease. His home medications were phenobarbital, aminophylline, and ranitidine.

We started major second-degree burn injury treatment, with fluid resuscitation according to the modified Burk formula. The patient was positive for Nikolsky's sign between affected skin lesions. Local treatment included wound debridement and application of petroleum jelly gauze and boric acid solution, every-day wound debridement and bandage, antibiotic therapy with vancomycin and cefepime according to sensitivity. Corticosteroids were excluded due to wound healing. We stopped phenobarbital and NSAID as they could possibly exacerbate TEN.

Our patient did not require mechanical ventilation. SCORTEN scale score on day one was 4, which remained the same on day three – SCORTEN scale score represented high mortality rate risk. A skin biopsy confirmed the diagnosis of TEN. After intensive treatment we noticed a decrease of rash and partial epithelization with skin pilling in the areas which were not involved.

We obtained verbal and signed consent of the patient 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.

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, as reported in some recent studies [12, 13, 14]. Further research is required before these markers can be reliably used for diagnosis [15, 16].

A recently published study shows a possible connection between TEN and a 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 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 intravenous immunoglobulin (IVIg) therapy for a part of the disease spectrum is not well documented. A consensus regarding combined corticosteroids and IVIg has not been reached. However, optimal therapeutic options such as systemic corticosteroids, IVIg, 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 systems with superficial major scald burns affecting 80% of the 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 interest: None declared.

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Приказ болесника са токсичном епидермалном некролизом са компликацијама и преглед литературе

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САЖЕТАК

Увод Токсична епидермална некролиза (ТЕН), позната и као Лајлов синдром, ретко је ексфолијативно обољење са веома високом стопом смртности. Овај ентитет је први описао Лајл 1956. године, и овај термин описује стање „токсичне епидермалне некролизе", апострофирајући на медикаметозно узроковану сензитивност као водећи механизам овог синдрома. Медикаменти који су најчешћи узрок овог синдрома су нестероидни антиинфламаторни лекови, хемотерапеутици, антибиотици, антиконвулзиви, али и вируси, бактерије и гљивице, као и имунизација.

Наш циљ је био да прегледом најновије литературе пронађемо оптималне терапијске модалитете за нашег болесника са ТЕН.

Приказ болесника Болесник, мушкарац старости 72 године, имао је бронхопнеумонију и повишену температуру пет дана, праћену болом у грлу. Лечен је антибиотицима и нестероидним антиинфламаторним лековима, након чега долази до развоја оспе и свраба по целом телу, као и развоја булозних промена на кожи, промена на мукози, конјунктивалне хиперемије, отежаног дисања и високе температуре, због чега је најпре био хоспитализован у локалној болници. Због прогресије булозних промена и погоршања општег стања болесник је пребачен у терцијалну здравствену установу и лечен у јединици интензивне неге под сумњом на ТЕН.

Закључак Сматрамо да болесници са ТЕН која захвата више од 80% површине тела, *SCORTEN* скором 4 и другим органским системима уз правовремено постављену сумњу на ТЕН могу бити успешно излечени.

Кључне речи: токсична епидермална некролиза; лековима индукована ТЕН; Одељење интензивне неге