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Treatment of allopurinol-induced toxic epidermal necrolysis with high dose corticosteroids and intravenous immunoglobulins

Allopurinol nedenli toksik epidermal nekrolizin yüksek doz kortikosteroidler ve intravenöz immünoglobulinler ile tedavisi

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Abstract

Toxic epidermal necrolysis (TEN) is an uncommon, acute and severe adverse reaction triggered by drugs, infections and malignancies. Drugs are the main cause of the disease. The most common drugs are sulfonamides and penicillins and the most often associated infectious agent is herpes simplex virus. Allopurinol is the first line drug for serum lowering therapy in gout and is approved by the US Food and Drug Administration (FDA). In recent studies, allopurinol was found to be the most commonly associated drug causing life-threatening drug reactions. Here, we aimed to present a rare case of TEN induced by allopurinol, the efficacy/harm of high dose systemic corticosteroids and use of intravenous immunoglobulins (IVIg) in the treatment of TEN.

Keywords: Toxic epidermal necrolysis, SCORTEN, Allopurinol, IVIg, Methylprednisolone

Öz

Toksik epidermal nekroliz (TEN), ilaçlar, enfeksiyonlar ve maligniteler tarafından tetiklenen nadir, akut ve ciddi bir advers reaksiyondur. İlaçlar hastalığın ana nedenidir. En yaygın ilaçlar sulfonamidler ve penisilinlerdir ve en sık ilişkili bulaşıcı ajan herpes simplex virüsüdür. Allopurinol, gutta serum düşürücü tedavi için ilk sıra ilaçtır ve ABD Gıda ve İlaç İdaresi (FDA) tarafından onaylanmaktadır. Son araştırmalarda, allopurinolün yaşamı tehdit edici ilaç reaksiyonlarına neden olan en yaygın ilişkili ilaç olduğu bulundu. Burada, allopurinolün neden olduğu nadir bir TEN vakası, TEN'in tedavisinde intravenöz immünoglobulinlerin kullanımı (IVIg) ve yüksek doz sistemik kortikosteroidlerin etkinliğini/zararlarını sunmayı amaçladık.

Anahtar kelimeler: Toksik epidermal nekroliz, SCORTEN, Allopurinol, IVIg, Metilprednizolon

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Introduction

Toxic epidermal necrolysis (TEN) is an uncommon, acute and severe adverse reaction which is characterized by necrosis of the epidermis [1]. Its incidence is approximately one per million a year and mortality rate is approximately 40% [2,3]. TEN is considered by a hypersensitivity reaction and triggered by drugs, infections and malignancies. The most common drugs are allopurinol, antibiotics, anticonvulsants, non-steroid anti-inflammatory drugs [1]. It is characterized by a rapidly progress which usually starts with a form of maculopapular rash, followed by atypical, targetoid erythematous or purpuric macules and bullous lesions on the skin. It can be accompanied by systemic symptoms and mucosal involvement. Fever, mild elevation of hepatic enzymes, intestinal and pulmonary manifestations can be seen [4]. A score called SCORTEN developed by Bastuji-Garin et al. [5] determines the variables as predictors of prognosis and risk of death in patients with TEN. Systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, plasmapheresis, antitumor necrosis factor drugs are the treatment options [6].

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Case presentation

A written consent was obtained from the patient before taking pictures and for using. An 85-year-old man patient initially noted the appearance of maculopapular rash and pruritus on his body. Over the next following 3 days, bullous lesions and exfoliation was started. He had a history of allopurinol taking before two weeks. Dermatological examination showed maculopapular rash in the extremities (Figure 1), diffuse erythema and exfoliation on the trunk (Figure 2) and scalp, large bullous lesions on the palmoplantar region (Figure 3). Oral and genital mucosa had erosion according to the seconder candida infection (Figure 4). He had atrial fibrillation, benign prostatic hyperplasia, hypertension, chronic renal failure and cerebrovascular accident as additional diseases. Histopathology showed subepidermal blister with confluent, full-thickness necrosis of the blister roof, reveals necrosis in all layers of the epidermis caused by apoptosis of keratinocytes and the dermis displays minimum inflammatory changes (Figure 5). SCORTEN score was 4. IVIg from 2gr/kg and methylprednisolone from 1mg/kg/day was started to the patient. IVIg doses divided into five consecutive days. Methylprednisolone was given for 24 days. After the treatment, the skin and mucosa findings completely healed. But pneumonia developed during treatment which may be caused by high doses of steroid. The drug reaction was resolved but he died from septic shock and pneumonia.

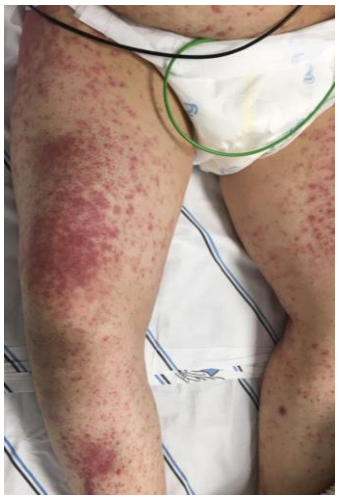

Figure 1: Maculopapular rash on the legs

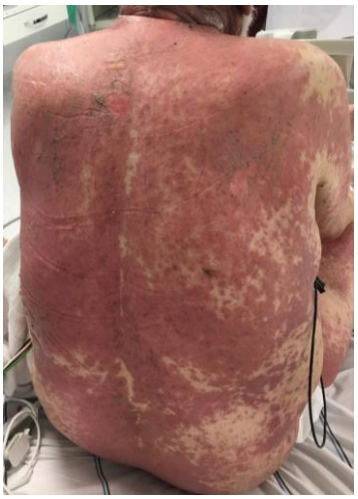

Figure 2: Maculopapular rash on the trunk

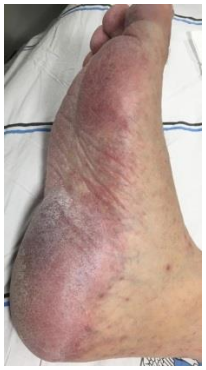

Figure 3: Large bullous lesion on the plantar region

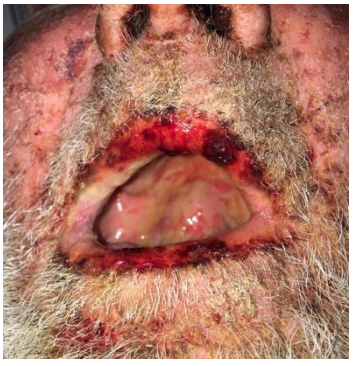

Figure 4: Erosions and hemorrhagic cruts in the oral mucosa

Discussion

TEN is a rare and serious reaction to life-threatening. The pathogenesis of the disorder is still unknown. Genetic sensitivity, antigen-specific immunity and the synthesis of mediators of cell death are thought to play a role in the development of the disease. It is considered as a T cell mediated type IV hypersensitivity disorder [7]. The necrosis occurs in kerophytocytes due to the death of keratinocytes with apoptosis. The binding of Fas (CD95), a membrane receptor present in keratinocytes, with its FasL ligand (CD95L), and the release of the perforin and granzyme B pathways are leading to apoptosis [1].

The drugs, infections and malignancies can play a role in the etiology. The 80% of TEN cases depend on drugs. Allopurinol is one of the most common drug in the development [1,8]. In our case, the disease was attached to allopurinol, too. It is commonly used in gouty arthritis and uric acid nephropathy to lower uric acid. However, allopurinol causes cutaneous adverse drug reactions. One study [8] reported a strong association of HLA-B*58: 01 with allopurinol-induced cutaneous adverse drug reactions.

SCORTEN score is used for disease prognosis [5]. It determines the probability of death. It is determined according to age, pulse rate, neoplasia status, body surface area, blood urea nitrogen, glucose, and bicarbonate levels [9]. The score was 4 in our patient.

Patients with TEN should preferably be treated in burn units. The first care should include supportive and symptomatic measures: body temperature control, hydration and electrolyte replacement, special attention to the airways, preventing secondary infection, pain control, maintenance of venous access distant from the affected areas, early oral nutrition or parenteral nutrition, if necessary, and anticoagulation [10]. Systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, plasmapheresis, anti-tumor necrosis factor drugs and N-acetylcysteine can be used in the treatment of skin lesions. Systemic corticosteroids were previously noted the treatment of choice, however there have been conflicting evidence with reported increased rates of infection, prolonged hospitalization and higher rates of mortality, while other studies have found some benefit [11]. In recent times, there have been numerous studies [12-14] that have supported the effectiveness and safety of IVIg. IVIg contains anti-Fas antibodies that inhibit the Fas/Fas ligand (FasL) interaction [6]. We used a combination of high dose systemic corticosteroids and IVIg because of higher age of patient and SCORTEN 4 in our case according to the study results.

In conclusions, we aimed to present this rare case because of draw attention to caution in terms of severe drug reactions when starting allopurinol and the efficacy/harm of high dose systemic corticosteroids and use of IVIg in the treatment of TEN.

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