Amoksisilinin Neden Olduğu Toksik Epidermal nekroliz

Toksik Epidermal Necrolysis Caused by Amoxicillin

Celalettin Sever, Yalçın Kulahcı, Sinan Oksuz, Haluk Duman
Department of Plastic and Reconstructive Surgery and Burn Unit, Gülhane Military Medical Academy and Medical Faculty, Haydarpasa Training Hospital, Istanbul, Turkey.

Özet
Toksik epidermal nekroliz (TEN), genelde ilaçlar ve enfeksiyonların neden olduğu ateş, stomatit ve konjonktivitin eşlik ettiği şiddetli bir cilt reaksiyonudur. Birçok ilacın TEN'e neden olduğu literatürlere bildirilmiştir ancak amoksisilinin neden olduğu TEN olgusunun literatürlere nadir olarak rapor edilmiştir. Bu olgu sunumunda, tonsilit tedavisinde reçetesi verilen amoksisilin kullanılarak bir bayan hastada gelişen TEN olgusu sunulmuştur. Son yıllarda enfeksiyonların tedavisinde amoksisillin yaygın olarak kullanılmaya başlaması, bu ilaca bağlı gelişen TEN olgularında görülen insidans artışını açıklamaktadır. Nadir olarak TEN'e sebep olan bir ilacın sitotoksik bir reaksiyona neden olduğunu açıklamak oldukça zordur.

Anahtar Kelimeler
Toksik Epidermal Necrolysis, Amoxicillin, Ilaç Reaksiyonu.

Abstract
Toxic epidermal necrolysis (TEN) is a severe skin reaction related to drugs and infections, characterized by fever, stomatitis and conjunctivitis. Many drug related TEN cases have been reported in literature but amoxicillin related TEN cases are rare. In this article, a case of amoxicillin related severe TEN in a female patient during treatment of tonsillitis has been reported. The increased use of amoxicillin, especially for control of infection, may be the reason for the increased incidence TEN due to the same drug. The identification of a drug as the cause for the immune related cytotoxic reaction may be difficult if the molecule is not generally known to be a classical cause of this reaction.

Keywords
Toxic Epidermal Necrolysis; Amoxicillin; Drug Reaction.

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Corresponding Author: Celalettin Sever, Selimiye Mah. Tıbbiye Cad. 34668 Kadıköy, İstanbul, Turkey.
Phone: +902165422656 · E-mail: drcsever@hotmail.com
**Introduction**

TEN is an acute life-threatening mucocutaneous reaction [1,2]. Most cases of TEN are drug induced. [3]. Other possible causes include immunization, viral infection, graft versus host disease, and connective tissue disorders.

The lesions of TEN are widely distributed erythematous macules, patches, stomatitis and conjunctivitis. Mucous membranes are involved in nearly all cases [4]. A clinical diagnosis is made with regard to pertinent history of an inciting agent and physical examination findings, including the extent of epidermal detachment and location of lesions [5]. The high mortality rate of TEN is caused either by infection or by respiratory distress, which is either due to pneumonia [6,7].

The first line of treatment is early withdrawal of culprit drugs, early referral and management in burn units. There are some advantages of burn intensive care unit treatment in TEN because the burn intensive care unit supports the patients with proper thermoregulations, intensive fluid replacement with electrolyte balance, enteral nutrition, infection control and wound management. For this reason, burn intensive care unit treatment in TEN provide a short healing time, short hospitalization, low morbidity and mortality rate.

We describe a patient who developed TEN after either administration of amoxicillin. Among other drugs, the reported reaction rates are relatively low for amoxicillin. In addition, the aim of the present study is to present the efficacy of the burn intensive care unit treatment with necessity in TEN.

**Case Report**

A 41 year old female nurse patient admitted to our burn centre with fever, generalised maculopapular rash and lip erosions one month after being drug reaction of amoxicillin. In this one monthly period, the patient was treated in intensive care unit of general surgery at another hospital. Her skin lesions got worse with extensive itchy painful blisters in both upper and lower extremities, neck, and anterior chest wall. This was associated with fever, malaise, and decreased oral intake. She was then admitted to our burn centre.

At our initial examination, second and third degree burn injury areas at body (~90% BSA) were noted (Figure 1A, 1B, 1C). In addition, there were aphthous lesions in the oral mucosa, the patient’s conjunctiva was hyperemic, and her ocular secretions were purulent (Figure 2). Ophthalmologic examination revealed bilateral conjunctivitis with no corneal involvement. A punch biopsy was taken from lesional skin on the abdominal region. Histological examination of the skin biopsy showed vesiculobullous reaction pattern with some areas showing full thickness epidermal necrosis consistent with a diagnosis of TEN. In subsequent days, she had fever and elevated white blood cell counts. Blood gas analyses and metabolic status were in critical limits. The clinical and laboratory signs of sepsis were determined and noted. Pseudomonas aeruginosa was cultured from the wounds and blood. There were respiratory distress signs and a chest
X-Ray demonstrated extensive bilateral pulmonary infiltrates (Figure 3). Immediate mechanical ventilation was performed. Unfortunately, she died from septic shock.

Discussion
TEN is severe, idiosyncratic reaction characterised by fever and mucocutaneous lesions that culminate in epidermal death and sloughing. Drugs cause adverse reactions which may occasionally be life threatening, such as Stevens-Johnson Syndrome (SJS) and TEN. Cases with skin surface involvement of 10% TBSA are diagnosed as SJS, while those showing involvement of 30% TBSA are called TEN. Epidermal detachment between 10% and 30% is classified as SJS/TEN overlap [8].

More than 100 drugs have been implicated as causes of SJS and TEN in case reports, but there is a very strong association with specific medications. While SJS may be caused by medications and/or infection, TEN is almost always drug induced. Common drugs implicated in TEN include sulfonamides, allopurinol anti-consulvants, and non-steroidal anti-inflammatory agents. In nearly 80% of cases, sulfonamides, anti-consulvants and allopurinol are the most consistently associated. The pathophysiologic mechanisms for SJS and TEN are still obscure but immunologic mechanisms, reactive drug metabolites and interactions between the two have been proposed.

Although most adverse reactions are transient, SJS and TEN may be persistent and are often accompanied with multi-organ failure. A clinical diagnosis is made with regard to pertinent history of an infecting agent and physical examination findings, including the extent of epidermal lesions [9]. Microscopically, there is sub-epidermal bullae formation, with eosinophilic epidermal necrosis. The dermal vessels show endothelial swelling without any vasculitis or necrosis. Ultra-structurally there is damage to the basal and lower spinous levels of the epidermis and cleft formation at the lamina densa [10].

Prognosis depends largely on the extent of skin involved. Complications include hypovolemic shock, pulmonary edema, acute tubular necrosis, membranous glomerulonephritis, gastrointestinal hemorrhage, bronchopneumonia and disseminated intravascular coagulation. Cicatricial alopecia, anonychia, ectropion, entropion and corneal opacities may also occur [11]. For this reason, prompt diagnosis and rapid initiation of supportive treatment remain the mainstay of management. Patients who have large full-thickness epidermal necrosis present a difficult management problem. They require the combination of intensive therapy facilities to support failing organs and specialized skin care, sometimes including extensive debridement and reconstruction. Treatment of TEN focuses on early withdrawal of the causative agent and referral of the patient to a burn center for critical care and appropriate wound management. Systemic therapy for TEN remains controversial with no standard guidelines available. Close fluid and electrolyte monitoring in an intensive care setting is optimal. Local care of the denuded skin areas is of utmost importance to avoid infection. Topical Chlorohexidine or Silver nitrate may be used to wash denuded areas. Silver sulfadiazine should be avoided due to the implications of sulfonamides in toxic epidermal necrosis. Bacterial cultures should be withdrawn and antibiotics started with the first sign of infection to prevent septicaemia. The use of systemic corticosteroids is very controversial and a consensus has not been reached so far; plasmapheresis, immunoglobulins and immunosuppressant drugs have been tried with non-conclusive results [11]. In addition, eye care with early referral to the ophthalmologist and oral care were instilled in all patients to avoid complications. Unfortunately, death is common, even if an intensive care is done. Half of the deaths occur due to secondary infection. Pulmonary edema, pulmonary embolism and gastrointestinal hemorrhage are other important causes of mortality [8,10,11]. Some measures should be taken to reduce incidence, morbidity and mortality rates of TEN.

1 ) It is important that both the patients and the medical personnel should take well planned education and this should be continuous and including every body. Awareness about the drugs implicated in life threatening drug reactions will help physicians in preventing them by judicious use of the drugs.
2 ) Uncontrolled drug selling by the drugstores should be prevented and especially antibiotics should not be sold without prescription. Drug manufacturers have to post warnings in their prospectus of the danger of potential reactions.
3 ) The management of TEN patients should be done burn centers because of their wide experience in managing burn wounds and their ability to provide infection control. In addition, a burns unit has, as part of the team, the allied staff to start early rehabilitation. This is a very important factor to ensure a good long-term outcome. Referral to a burns team should be considered as a treatment option by clinicians dealing with such cases.

We hope that this case report will succeed in raising awareness of the dangers of TEN due to antibiotics.

References