

An Uncommon Dermatologic Emergency Caused by a Commonly Prescribed Drug

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Abstract

Seventy six years old man with history of arterial hypertension and gout brought to the emergency room due to pruritic maculopapular rash starting two days before admission. First noted at his back, then progressively distributed throughout the body. He was taking allopurinol for gout. Physical exam revealed an acutely ill patient, somnolent, but oriented in 3 spheres. Vital signs showed tachycardia, tachypnea, and borderline low arterial blood pressure. He had swelling of tongue, lips, eyelids, as well as oral ulcers. His condition deteriorated with skin detachment of 90% of surface area. Also presented altered mental status and hypoxemia requiring endotracheal intubation. Intravenous gammaglobulin was administered as well as 6 liters of intravenous fluids. Skin wounds were covered with appropriate dressing, and he was transferred to Intensive Care Unit. The patient was diagnosed with Toxic Epidermal Necrolysis (TEN), confirmed by skin biopsy which shows epithelial necrosis. Unfortunately 2 days later he died.

TEN is a dermatologic emergency that is characterized by an acute epidermal necrosis. It is determined by the percent of body surface area with epidermal detachment involving greater than 30%. Up to 80% of cases of TEN are drug related. In the United States the annual incidence is around 0.22 to 1.23 cases per 100,000 population. Mortality rate approaches 40% to 50%.

The patient suffered from TEN secondary to allopurinol, a common prescribed drug. The majority of drug reactions that we commonly see at the emergency room are minor skin reactions or even angioedema, but rarely TEN. It is an impressive reaction that we have to treat aggressively, similar to third degree burns. Most common causes of death are from complications such as dehydration, infections and respiratory compromise. A complete history and physical exam is essential to find the etiologic agent and provides prompt management in order to decrease mortality.

Introduction

The skin is considered the largest organ in the human body [1]. Consist of three principal layers; the epidermis, dermis and the hypodermis. Many functions are attributed, it served as our first and biggest barrier that protect us from microorganism, helps regulate body temperature, and permits the sensations of touch, heat, and cold. It is also responsible of nutrient absorption, among others [1]. The most common pathologies affecting skin are acne, infections, traumas and rash. However life threatening condition such as Toxic epidermal necrolysis is uncommon [1]. Toxic Epidermal Necrolysis (TEN) and Stevens - Johnson syndrome (SJS) are severe skin reactions, most commonly triggered by drugs [2]. TEN involves greater than 30% of skin detachment [2]. Mortality may be as high as 40 to 50% [3]. Estimates of incidence range from two to seven cases per million people per year, with no age predominance.

Case

76 years old man with arterial hypertension, dislipidemia and gout. He noticed swelling of his right leg and knee of approximately four days of evolution and was treated with Allopurinol. However 2 days afterwards he noticed an erythematous maculopapular pruritic rash; first at his back but progressively distributed throughout the body. Also presented unquantified fever and chills. Denies dyspnea, chest pain, nauseas or vomiting. As skin lesions spread, his eyes and oral mucosa were involved. Physical exam was remarkable for an acutely ill patient, somnolent, but oriented in 3 spheres. Vital sighs showed tachycardia (122 beat per minute), tachypnea (22 breaths per minute), and border line low arterial blood pressure (100/60 mmHg). Swelling of tongue, lips, eyelids, as well oral ulcers were prominent findings (Figure 1). His condition deteriorates with 90% skin detachment (Figures 2 and 3). He presented altered mental status and hypoxemia

requiring endotracheal intubation to protect his airway. Patient was evaluated by a multidisciplinary team. Skin biopsy confirmed TEN (Figure 4) showing epithelial necrosis. Ophthalmology evaluation revealed corneal abrasion. Intravenous gammaglobulin was started as well coverage of affected skin areas with petrolatum impregnated gauzed and Garamycin eye drops for corneal abrasion. As his condition worsened Vancomycin 15 mg/kg intravenously and Cefepime 2

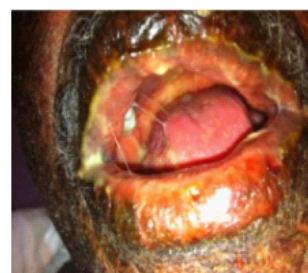


Figure 1: Perioral dryness with mucosal involvement.

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grams intravenously were ordered to cover broad spectrum organism including *Pseudomonas*. Aggressive fluid resuscitation was provided, we use the parkland formula to determine affected area and calculate intravenous hydration with isotonic normal saline. Eventually was transferred to the intensive care unit of our institution where he received close monitoring. Basic metabolic panel and cell body count were among basic laboratories ordered (Tables 1 and 2) which shows deterioration since his admission. However despite aggressive management patient died 3 days after admission.

Discussion

Toxic Epidermal Necrolysis (TEN) and Stevens - Johnson syndrome (SJS) are severe skin reactions, most commonly triggered by medications such as allopurinol, sulfonamides, penicillin, cephalosporins, carbamazepine, dilantin, lamotrigine, phenobarbital among others [4]. Allopurinol which is a commonly prescribed drug is considered the offending drug used by our patient. He presented fever, malaise, rash manifested as erythematous macules and patches with mucocutaneous lesions leading to necrosis and detachment of the epidermis.

The exact mechanism responsible for above pathology is not completely understood. Several theories about TEN etiology have been proposed, however immunologic processes seem to be the basic pathology [5]. Granulysin, a cytolytic protein produced and secreted by cytotoxic T lymphocytes and natural killer (NK cells),



Figure 2: Skin detachment (Nikolsky sign).



Figure 3: Patient back showing skin detachment with exposure of dermis.

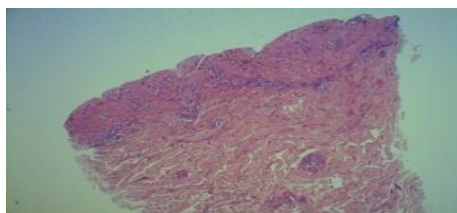


Figure 4: Skin biopsy: Shows epithelial necrosis.

CBC	Day #1	Day #3	Normal range
WBC	8.1 x10 ³ /μl	1.8x 10 ⁹ /L	3.8-10.8x10 ⁹ /L
Hgb	11.2 mg/dl	9 g/dL	Male: 13.8-17.2 g/dL Female:12-15.6 g/dL
HCT	33.5%	30%	Male:41-50% Female:35-46%
PTL	157μl	83X10 ⁹ /L	150-450x10 ⁹ /L
NE	76%	89%	35-80%

Day #1 . Admission day
Day #3. Decease day

Table 1: CBC

	Day #1	Day #3	Normal range
Sodium	145mEq/L	133mEq/L	135-145 mEq/L
Potassium	5.0mEq/L	5.3mEq/L	3.5-5 mEq/L
Chloride	107mEq/L	103mEq/L	95-108 mEq/L
CO ₂	20mmol/L	16mmol/L	20-32 mmol/L
BUN	23mg/dl	46mg/dl	2.5-10.7 mg/dl
Creatinine	0.9mg/dl	2.3mg/dl	0.7-1.4 mg/dl
Glucose	245mg/dl	263mg/dl	<110 mg/dl
IgA	399 mg/dl (NV: 68-378)		

Day #1 Admission day
Day #2 Decease day

Table 2: Chemistry and special labs.

could be implicated [5]. Also genetic factors have been shown to play a role; among those associated with an increase risk of TEN include: HLA-B*1502 and HLA-B*3101 which are associated with increased risk of TEN due to carbamazepine and other aromatic anticonvulsants. Other mechanisms that have been proposed are: Polymorphism in IL4 receptor which is linked to cytokine inflammation, low N-acetylation capacity and malignancy.

TEN is a rare disease. The approximated incidence in adult population is between 0.4 and 1.2 cases per 1 million people per year. For unknown reasons female predominance has been noted however other groups as HIV patients and the elderly are at increased risk. The mortality rate of TEN may exceed 30% whereas SJS is about 5%. Mortality is increased significantly in patients who are at the extremes of age, HIV patients and is proportional to the percentage of denuded skin (affected area). The most common cause of death in this condition is sepsis. Among the most common and deadly pathogens associated with sepsis in those patients are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Treatment of TEN should focus on early identification, withdrawal of the causative agent and referral of the patient to a burn center or intensive care unit. Multidisciplinary team care is highly recommended to provide aggressive treatment. Local and wound care of the denuded skin areas is of essential to avoid infection. Bacterial cultures should be withdrawn upon admission even though use of antibiotic prophylaxis is considered controversial. Antibiotics should be started with the first sign of infection to prevent septicemia. Early protections of airways, aggressive hydration as well as ophthalmic and dermatologic evaluations are valuable for diagnosis and treatment. Others approaches for systemic management of TEN has been proposed as use of corticosteroids, plasmapheresis and immunoglobulin nevertheless controversial results have been reported.

Conclusion

As mentioned through this presentation TEN is a very rare but deathful complication in medicine. Even though we are not use to

manage this condition in our routine practice we must be aware for early identification and prompt management. The most crucial interventions in TEN are discontinuation of the offending drug and intensive supportive care in a burn unit in order to decrease mortality [6]. Supportive care should be the primary focus in the management of TEN but also a multidisciplinary team must be included to provide appropriate care.

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