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Case Report

ALLOPURINOL INDUCED STEVEN- JONSON SYNDROME: CASE REPORT

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ABSTRACT
Adverse drug reactions occur in about 0.3 to 7% of all hospital admissions and are associated with high morbidity and mortality. Their presentation varies from mild rashes to severe reactions such as Stevens-Johnson syndrome (SJS). Steven Johnson's Syndrome is rare, serious systemic disorder involving the skin and mucous membranes. Stevens-Johnson syndrome is commonly associated with adverse drug reaction, but can be associated with infection or combination of infection and adverse drug reactions. This case report describes sever Stevens-Johnson syndrome in a patient after receiving allopurinol therapy for Gouty arthritis.

Keywords: *Allopurinol; Stevens-Johnson Syndrome; Drug Reactions*

INTRODUCTION
Adverse cutaneous drug reactions are common, affecting 3-5% of hospitalized patients with approximately 1 in 1000 hospital patients suffer from life-threatening cutaneous drug reactions (Roujeau, 1994; Fiszenson *et al.,* 2003). Drugs most commonly implicated in adverse cutaneous reactions are anticonvulsants, antibiotics, NSAIDs and antirheumatic drugs (Tomy, 2012).
Allopurinol, which is an effective uric acid-lowering drug, has been implicated in many life threatening severe adverse drug reactions including hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (Halevy *et al.,* 2008). The risk of allopurinol-associated cutaneous reaction was assessed in 4 European countries from 1989 to1993.
Allopurinol treatment was recorded in 13 of245 patients with SJS or TEN (5.3%) and in 11 of 1147 control subjects (1%) (Roujeau *et al.,* 1995). Again, the risk of allopurinol-associated SJS or TEN was re-evaluated in a new European case-control study (EuroSCAR) conducted from 1997 to 2001 (Mockenhaupt *et al.,* 2007).
Results from multinational case-control study showed that; daily dose of 200mg or more of allopurinol was associated with an increased risk for SJS or TEN (adjusted OR = 36, 17-76) compared with lower daily doses (3.0, 1.1-8.4) (Halevy *et al.,* 2008). However, there was no association between the severity of illness, as manifested by the maximal erythema, the maximal detachment of the epidermis, or death and the daily dose of allopurinol.
The pathogenesis of SJS is not yet well known. A cell-mediated cytotoxic reaction against keratinocytes leading to massive apoptosis has been suggested in early studies (Borchers *et al.,* 2008). Recent studies demonstrated that cytotoxic T-cells are drug-specific and directed against the native form of the drug rather than against a reactive metabolite (Roujeau and Bricard, 2011).
A systematic review and meta-analysis, in both Asian and non-Asian populations, found a significant association between human leukocyte antigen, HLA-B*5801, and allopurinol-induced SJS/TEN (Somkrua *et al.,* 2011).
The disease is diagnosed clinically. Fever >38°C (100.4°F), skin tenderness, mucositis, and blistering usually alert the possibility of Stevens-Johnson syndrome (Bircher, 2005). The skin lesions typically begin with ill-defined, coalescing erythematous macules with purpuric centers, although many cases of SJS may present with diffuse erythema (Schwartz and McDonough, 2013). Mucosal involvement occurs in most cases of SJS and even may precedes the onset of skin lesions (Roujeau, 1994). Oral and ocular mucosa is of particular important and is associated with severe consequences (Gueudry *et al.,* 2009).

CASES

A 40 year- old man presented to the out-patient clinic with joint symptoms, mainly of the lower limbs. Upon the clinical presentation and laboratory tests he was diagnosed as gouty arthritis and started on oral allopurinol 3oo mg daily. Three weeks later the patient developed itchy diffuse skin lesions initially in the face and thorax then extended to other areas. Within two days the patient developed conjunctival itching with eye discharge, and swelling of the eye lids. He also experienced difficulties in swallowing and speech, associated with excessive salivation. Patient appeared ill, but vital signs were normal. There were obvious drooling of saliva, angular stomatitis, crusted lips, and painful hemorrhagic erosions covered with white membrane on the oral mucosa (Figure 1). The conjunctiva appeared congested, and there were purulent discharge and some target lesions on the eye angles (Figure 2). Erythematous macules and papules, of different size, with dark- brown centers, described as typical target lesions, were seen bilaterally, predominantly, in the face and upper trunk (Figure 3). Nikolsky's sign was positive. The diagnosis of Steven Johnson's syndrome was made based on the clinical presentation and the history of allopurinol exposure. Laboratory examination revealed mild leukocytosis, and alanine aminotransferase, C-reactive protein, and potassium were mildly elevated. Serological test for HIV returned negative. The patient was admitted and allopurinol was withdrawn immediately. Supportive care in form of, fluid and electrolyte management, nutritional support, ocular care, and pain control, was started. Patient showed dramatic improvement and the skin lesions started to slough leaving extensive skin denudation (Figure 4). However, during the hospital stay patient developed irritating cough, associated with mild grade fever, malaise, and loss of appetite. Respiratory rate was 20/min, and chest examination revealed scattered crackles and expiratory wheezes. Chest X ray was normal.

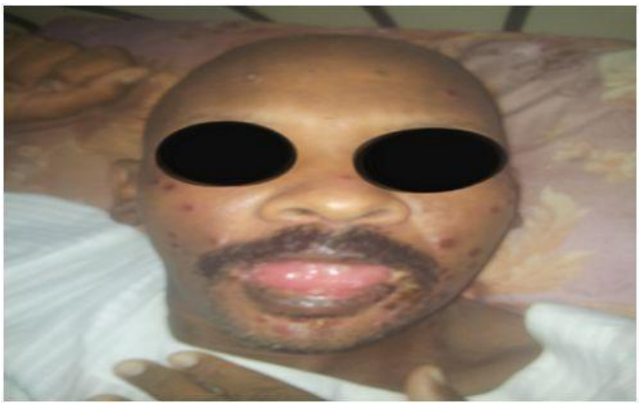

Figure 1: Multiple erosions and crusts are present in the oral cavity of this patient. There are hemorrhagic erosions covered with white membrane on the oral mucosa

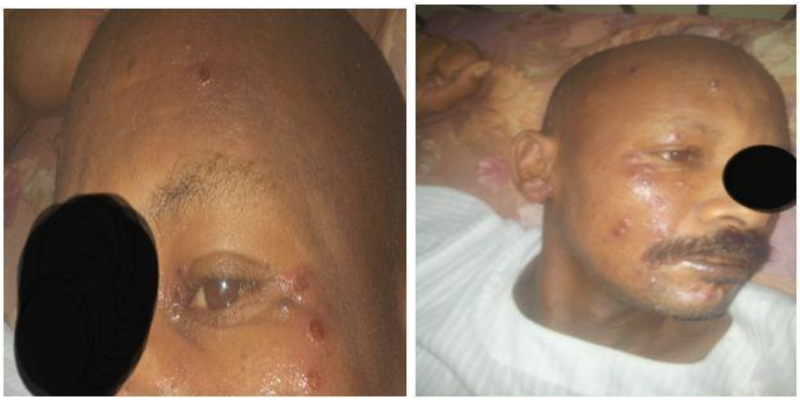

Figure 2: Swelling of the eye lid and congestion of the conjunctiva. Target lesions appeared in the corners of the eye, bilaterally

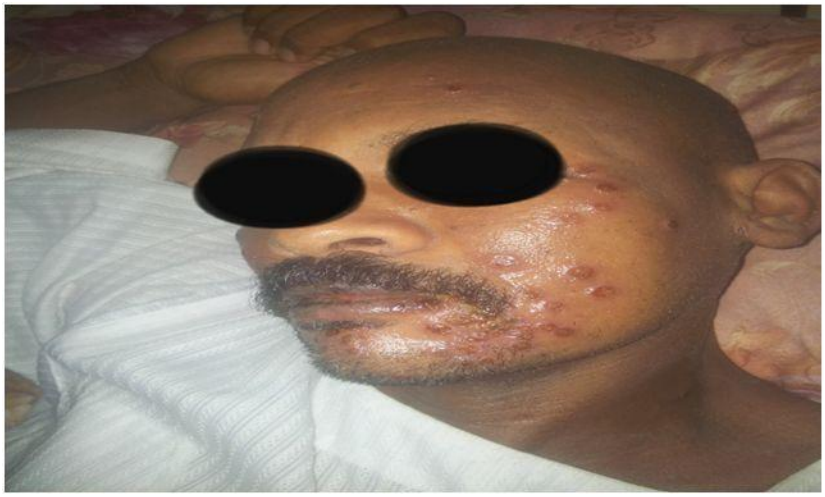

Figure 3: Target like lesions with dark brown centre, distributed symmetrically in many areas, started on the face and upper trunk

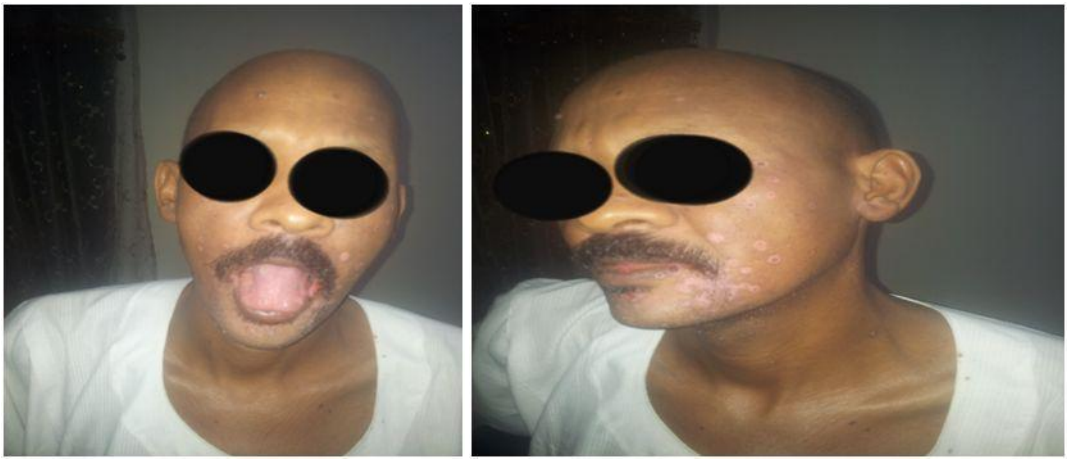

Figure 4: Sloughing of the skin, leaving extensive denudation. Oral mucosal changes regress completely

Diagnosis of interstitial pneumonia as a complication of SJS was made and the patient respond well to the combination of Co amoxiclav and Tetracycline therapy. Patient discharged after 10 days in a good condition.

DISCUSSION

Stevens-Johnson syndrome (SJS) is severe mucocutaneous reactions, most commonly triggered by medications, characterized by extensive necrosis and detachment of the epidermis. It is more common in HIV-infected individuals (Mittmann *et al.,* 2012). SJS can occur in any age, and it is more common in women than in men (Sekula *et al.,* 2013). Allopurinol is the most common cause of adverse drug reactions in many previous studies (Sekula *et al.,* 2013; Lin *et al.,* 2005). The incidence of allopurinol induced SJS is increased, due to increase use and dosages of allopurinol (Fam *et al.,* 2001). SJS can be triggered by drugs other than allopurinol like, anticonvulsants, antibiotics, NSAIDs and antirheumatic drugs (Tomy, 2012). The patient in this report developed adverse reactions in the third week after exposure to allopurinol. This is in keeping with the results from multinational case-control study that revealed the risk for SJS was restricted to recent users (less than 8-week interval between initiation of treatment and onset of reaction) (Halevy *et al.,* 2008).

The risk for allopurinol induced SJS could be dose dependent. Previous reports showed that adverse reactions to allopurinol are dose dependent (Fam *et al.,* 2001). EuroSCAR study reported that, both recent initiation of allopurinol treatment and high allopurinol dose, was associated with increased risk of allopurinol induced SJS.

Infections are the next most common trigger of SJS, particularly in children and young adult (Wetter, 2010). Mycoplasma pneumonia has been cited as the most common infectious cause. Patients with infection induced SJS, usually have upper respiratory tract symptoms preceded the onset of skin rash (Tsai and Oman, 2011), and the disease is associated with less severe complications and less internal organ involvement (Wetter, 2010).

Pulmonary complications, including pneumonia and interstitial pneumonitis, are frequent in drug induced SJS. Acute respiratory failure requiring mechanical ventilation has been reported in approximately 25 percent of patients with SJS (De Prost *et al.,* 2014). Treatment options for SJS are limited and controversial (Roujeau, 1994). However, it's generally agreed that, early identification and withdrawal of the offending agent may improve the prognosis of SJS, especially after exposure to drugs with short half-lives (Garcia-Doval *et al.,* 2000). Supportive care is the mainstay of treatment and includes fluid and electrolyte management, nutritional support, wound care, ocular care, temperature management, pain control, and monitoring or treatment of infection (Schwartz and McDonough, 2013). Several immunosuppressive or immune-modulating therapies have been used in clinical practice, including intravenous immune-globulins (IVIG), systemic corticosteroids, plasmapheresis, and anti-TNF monoclonal antibodies. However, none have been adequately studied in randomized trials (Schneck *et al.,* 2008). Previously reported that in up to 86% of treated patients, allopurinol is inappropriately prescribed (Zell, 1989; Singer, 1986), so rational use of allopurinol according to the guidelines (Smith and Karlson, 2000) could lead to a significant decrease in morbidity and mortality from allopurinol-associated SJS.

Conclusion

Steven johnson syndrome is rare, serious systemic disorder commonly associated with adverse drug reaction**.** Allopurinol is the most common cause of adverse drug reaction, including Steven johnson syndrome. This case is especially interested as it is associated with pulmonary complications in addition to the common ocular and cutaneous complications of steven Johnson syndrome.

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