Amoxycillin and clavulanic acid induced Stevens-Johnson syndrome: a case report

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INTRODUCTION

Stevens-Johnson syndrome (SJS) is an immune complex mediated hypersensitivity complex that typically involves the skin and the mucous membranes. Although several classification schemes have been reported, the simplest classification breaks the disease down as follows:

- Stevens-Johnson syndrome; a minor form of toxic epidermal necrolysis, with less than 10% body surface area (BSA) detachment
- Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis; detachment of 10-30% of the BSA
- Toxic epidermal necrolysis; detachment of more than 30% of the BSA.

While minor presentations may occur, significant involvement of oral, nasal, eye, vaginal, urethral, gastrointestinal, and lower respiratory tract mucous membranes may develop in the course of the illness. GI and respiratory involvement may progress to necrosis. Stevens-Johnson syndrome is a serious systemic disorder with the potential for severe morbidity and even death.

ABSTRACT

Stevens-Johnson syndrome (SJS) is an immune complex mediated hypersensitivity complex that typically involves the skin and the mucous membranes. Various etiologic factors (e.g., infection, drugs and malignancies) have been implicated as causes of Stevens-Johnson syndrome. However, as many as half of the cases are idiopathic. Bastuji and Roujeau proposed that the denomination of Stevens-Johnson syndrome should be used for a syndrome characterized by mucous membrane erosions and widespread small blisters that arise on erythematous or purpuric macules that are different from classic targets. In this case report, a 6 year old girl who was administered a cough syrup (containing bromhexine, guaiphenesin, diphenhydramine and phenylephrine) and amoxycillin and clavulanic acid dispersible tablet for the treatment of cough developed pruritic skin eruptions all over the body along with painful erosions on the tongue, buccal mucosa, genital and anal mucosa. A diagnosis of Stevens-Johnson syndrome was made. Amoxycillin and clavulanic acid combination was identified as the culprit based on the temporal relationship between the drug administration and the appearance of the rashes and based on a number of SJS reports implicating amoxycillin and clavulanic acid having been published before. The cough syrup and amoxycillin and clavulanic acid combination tablets were immediately stopped. Symptomatic treatment was administered. The child improved and was later discharged. Causality assessment using Naranjo adverse drug reaction probability scale revealed that amoxycillin and clavulanic acid combination was a possible cause for the harmful cutaneous adverse reaction with a score of 4.

Keywords: Stevens-Johnson syndrome, Amoxycillin and clavulanic acid, Bromhexine, Guaiphenesin, Diphenhydramine, Phenylephrine, Mucous membrane erosions, Erythematous macules, Purpuric macules, Blisters, Naranjo Adverse Drug Reaction Probability scale
The syndrome was first described in 1922, when the American pediatricians Albert Mason Stevens and Frank Chambliss Johnson reported the cases of 2 boys aged 7 and 8 years with "an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis." Both cases had been misdiagnosed by primary care physicians as hemorrhagic measles.

Since 1983, erythema multiforme major and Stevens-Johnson syndrome had been considered synonymous. In the 1990s, however, Bastuji and Roujeau each proposed that erythema multiforme major and Stevens-Johnson syndrome are 2 distinct disorders. They suggested that the denomination of erythema multiforme should be restricted to patients with typical targets or raised edematous papules, with or without mucosal involvement. This clinical picture is in accordance with the original description by von Hebra.

Bastuji and Roujeau further proposed that the denomination of Stevens-Johnson syndrome should be used for a syndrome characterized by mucous membrane erosions and widespread small blisters that arise on erythematous or purpuric maculae that are different from classic targets.

According to this clinical classification, erythema multiforme major and Stevens-Johnson syndrome could be 2 distinct disorders with similar mucosal erosions, but different patterns of cutaneous lesions. This hypothesis is supported further by a strong correlation between clinical classification and the probable cause.

Various etiologic factors (e.g., infection, drugs and malignancies) have been implicated as causes of Stevens-Johnson syndrome. However, as many as half of the cases are idiopathic. There is strong evidence for a genetic predisposition to Stevens-Johnson syndrome provoked by certain drugs. There are no specific laboratory studies (other than biopsy) that can definitively establish the diagnosis of Stevens-Johnson syndrome. No specific treatment of Stevens-Johnson syndrome is noted; most patients are treated symptomatically. In principle, the symptomatic treatment of patients with Stevens-Johnson syndrome does not differ from the treatment of patients with extensive burns. Withdrawal of the suspected offending agent is critically important. Immunomodulatory treatment is controversial.

**CASE REPORT**

A 6 year old girl was brought by her parents to the paediatrics out-patient department with itchy skin eruptions all over the body. The parents gave a history of cough in the child for which she was administered a cough syrup (containing bromhexine, guaifenesin, diphenhydramine and phenylephrine) and a fixed combination of amoxycillin and clavulanic acid dispersible tablets (228.5 mg). The eruptions were seen in the morning (the night before she was administered amoxycillin and clavulanic acid). The cough syrup was administered in the afternoon and the evening of the day before the day eruptions started to appear. Fever was also seen in the child. The eruptions were erythematous, target-like, round lesions with central pale area. The eruptions were 2-3 cm in diameter and present throughout the body, more concentrated on the upper and lower limbs, upper chest, abdomen, palms and soles (Figures C and D). The eruptions were minimal on the back, and the face and scalp were spared. On examination, erosive lesions were present on the lips, buccal mucosa and the tongue, which were painful (Figure A). Painful erosions were also seen on the genital mucosa. A sticky, purulent discharge was seen from the eyes (Figure B). A diagnosis of Stevens-Johnson syndrome was made.

![Figure 1: Amoxycillin and clavulanic induced Stevens-Johnson syndrome; A) painful erosions on the lips; B) mucopurulent conjunctivitis; C) erythematous macules on the palms; D) crusting cutaneous blisters on the chest and abdomen.](image-url)

Amoxycillin and clavulanic acid tablet was immediately stopped. The cough syrup was also stopped immediately.

Subsequently, multiple vesicles and bullae with antral necrosis developed in the area of the lesions. Blistering of the lesions was noted. Swelling of the face and lips were noted. There were episodes of bleeding from the oral cavity. A slough and whitish plaques were observed over the lesions.
the tongue. The lesions later crusted on the skin and the oral cavity.

Bleeding time and clotting time were in the normal limits. Absolute eosinophil count was normal. Blood urea and serum creatinine levels were normal. Liver function tests were normal. Urine culture revealed growth of E.coli. Sensitivity of the E.coli strains towards gentamicin, cotrimoxazole and cefepime was noted.

The following drugs were administered to the child.

- Injection dexamethasone 0.5 ml (2 mg) i.v for 7 days and later put on tablet prednisolone 10 mg once a day.
- Cream containing mometasone furoate and fusidic acid was applied topically on the eruptions.
- Syrup paracetamol (250 mg/5 ml)-4 ml four times a day.
- Syrup cetirizine 5 ml at night.
- Candid ( clotrimazole) mouth paint on the white plaques in the oral cavity.
- FML-T eye drops (fluorometholone 0.1% and tobramycin 0.3%) one drop 6th hourly in both the eyes.
- Eye mist gel (hydroxypropylmethylcellulose) in both the eyes fourth hourly.
- Intravenous dextrose normal saline.
- Rexidine (chlorhexidine) mouth wash was prescribed.
- Injection gentamicin 45 mg i.v twice a day.
- Injection pantoprazole 10 mg i.v once a day.
- Botroclot (botropase) local application on the bleeding lesions in the oral cavity for the first 2 days.
- Azithromycin syrup 100 mg once a day orally advised from day 8 for 3 days.

The child improved with the above treatment and was subsequently discharged from the hospital with the advice not to be administered beta-lactam antimicrobials in the future.

**DISCUSSION**

Various etiologic factors have been implicated as causes of Stevens-Johnson syndrome. Drugs most commonly are blamed. The 4 etiologic categories are infectious, drug-induced, malignancy-related and idiopathic. Stevens-Johnson syndrome is idiopathic in 25-50% of cases. Drugs and malignancies are most often implicated as the etiology in adults and elderly persons. Pediatric cases are related more often to infections.

Viral diseases that have been reported to cause Stevens-Johnson syndrome include herpes simplex virus (possibly, remains a debated issue), AIDS, coxsackie viral infections, Influenza, Hepatitis and Mumps.

In children, *epstein-barr* virus and *entero* viruses have been identified. More than half of the patients with Stevens-Johnson syndrome report a recent upper respiratory tract infection.

Bacterial etiologies include group A beta-hemolytic streptococci, diphtheria, brucellosis, lymphogranuloma venereum, mycobacteria, mycoplasma pneumonia, rickettsial infections, tularemia and typhoid.

Possible fungal causes include coccidioidomycosis, dermatophytosis and histoplasmosis. Malaria and trichomoniasis have been reported as protozoal causes.

Antibiotics are the most common cause of Stevens-Johnson syndrome, followed by analgesics, cough and cold medication, NSAIDs, psychoepileptics and antigout drugs. Of antibiotics, penicillins and sulfa drugs are prominent; ciprofloxacin has also been reported.

The anticonvulsants implicated are phenytoin, carbamazepine, oxcarbazepine, valproic acid, lamotrigine and barbiturates.

Mockenhaupt et al stressed that most anticonvulsant-induced SJS occurs in the first 60 days of use.

Antiretroviral drugs implicated in Stevens-Johnson syndrome include Nevirapine and possibly other non-nucleoside reverse transcriptase inhibitors. Indinavir has been mentioned.

Stevens-Johnson syndrome has also been reported in patients taking modafinil, allopurinol, mirtazapine, tnf-alpha antagonists (eg, infliximab, etanercept, adalimumab), cocaine, sertraline, pantoprazole, tramadol.

There is strong evidence for a genetic predisposition to severe cutaneous adverse drug reactions such as Stevens-Johnson syndrome. Carriage of the following human leukocyte antigens has been associated with increased risk: HLA-B*1502, HLA-B*5801, HLA-B*44, HLA-A29, HLA-B12, HLA-DR7, HLA-A2, HLA-B*5801, HLA-A*0206, HLA-DQB1*0601.

Certain of these HLA alleles are associated with an increased probability of developing Stevens-Johnson syndrome upon exposure to specific drugs. The US food and drug administration (FDA) and health Canada advise screening for HLA-B*1502 in patients of south eastern Asian ethnicity before starting treatment with carbamazepine. (The risk is much lower in other ethnic populations, making screening impractical in them). HLA-B*5801 confers a risk of allopurinol-related reactions. Pretreatment screening is not readily available.

Whites with HLA-B*44 appear to be more susceptible to develop Stevens-Johnson syndrome. HLA-A29, HLA-
B12, and HLA-DR7 are frequently associated with sulfonamide-induced Stevens-Johnson syndrome, while HLA-A2 and HLA-B12 are often encountered in Stevens-Johnson syndrome induced by non-steroidal anti-inflammatory drugs (NSAIDs).\(^2\)

HLA-A*0206 and HLA-DQB1*0601 allele have been shown to be was strongly associated with Stevens-Johnson syndrome with ocular disease.

Nevertheless, whether the presence of those genes constitutes a predisposition to Stevens-Johnson syndrome or whether those genes are in linkage disequilibrium with more relevant adjacent genes is unknown.\(^1\)

Antigen presentation and production of tumor necrosis factor (TNF)-alpha by the local tissue dendrocytes results in the recruitment and augmentation of T-lymphocyte proliferation and enhances the cytotoxicity of the other immune effector cells.\(^12\) A "killer effector molecule" has been identified that may play a role in the activation of cytotoxic lymphocytes.\(^13\) The activated CD8+ lymphocytes, in turn, can induce epidermal cell apoptosis via several mechanisms, which include the release of granzyme B and perforin.

The death of keratinocytes causes separation of the epidermis from the dermis. Once apoptosis ensues, the dying cells provoke recruitment of more chemokines. This can perpetuate the inflammatory process, which leads to extensive epidermal necrolysis.\(^14\)

Amoxycillin and clavulanic acid combination therapy was identified as the causative agents because of the temporal relationship between the administration of the combination and the beginning of the eruptions.

There have also been several other previous reports linking amoxycillin and clavulanic acid to Stevens-Johnson syndrome.

In this clinical scenario, causality assessment using Naranjo adverse drug reaction probability scale revealed that amoxycillin and clavulanic acid induced SJS was possible (A score of 4).

CONCLUSION

The child was diagnosed with Stevens-Johnson syndrome and the possible cause was traced to amoxycillin and clavulanic acid medication. The parents were advised to carry the information card and never to administer beta-lactam antimicrobials to the child in the future.

Clinicians should be conscious of the risk of amoxicillin and clavulanic acid-induced SJS in children in order to avoid a fatal outcome. Management involves early identification, withdrawal of the culprit drug and rapid initiation of supportive therapies.

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