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CASE REPORT

Diclofenac-Induced Stevens-Johnson Syndrome: A Case Report

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ABSTRACT

Drugs are an important cause of Stevens–Johnson syndrome (SJS) in about 95% of reports. 100 drugs have been reported as causes of SJS or toxic epidermal necrolysis (TEN). There are very few reports of SJS due to use of diclofenac. In this report we present a 65 year old lady who developed SJS after usage of diclofenac suppository.

Keywords: *Stevens–Johnson syndrome, Diclofenac, Drug reaction*

Toxic epidermal necrolysis and Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) are acute life-threatening conditions. TEN causes erosions of the mucous membranes, extensive detachment of the epidermis, and severe constitutional symptoms [1]. The incidence of TEN is estimated at 1 to 6 cases per million person-years [2]. It is thought that syndrome is a hypersensitivity complex that affects the skin and the mucous membranes. Although the majority of cases are idiopathic (without a known cause), the main class of known causes is medication, followed by infections and, rarely, cancers [3]. Drugs are an important cause of SJS in about 95 % [4]. Infections or a combination of infections and drugs have also been reported as the ethiology of the syndrome [5]. In case reports and studies, more than 100 drugs have been reported as causes of SJS or TEN [1,2].

Today, drug therapy for the control of pain has been encountered a great problem because of drugs' serious adverse reactions. Although Non-steroidal anti-inflammatory drugs (NSAIDs) are a rare cause of SJS in adults, these risks should be npot ignored. This risk is higher for older patients, women and those in the beginning of the treatment [3]. Typically, the symptoms of drug-induced SJS arise within a week of starting the medication. With use of piroxicam or tenoxicam, the estimated incidence of TEN or SJS is one per 100,000 patients during the first eight weeks of treatment [6].

CASE REPORT

A 65-year-old female patient came to our hospital with complaints of multiple ulcerations in skin, burning sensation in the oral cavity and conjuctivitis. On physical examination, some reddish-based lesions were distributed on the right and left buccal mucosa, floor of the mouth and surface of the tongue. In addition, she had reddish purple maculopapular lesions on the back and forearms (Fig 1). Totaly her skin lesions were despread on less than 10% of body surface area. Ulceration was also focused on conjunctiva, nasal mucosa and lips. All of these leaded us to probability of the diagnosis of SJS. We ruled out all infectious causes of SJS with clinical examination, history taking, nessecary serological test and bacteriological culture. Skin biopsy was done but we did not waite for its result.

In her drug history, we found that she has used diclofenac suppository 100 mg twice a day for one month due to her joint pain. We immediately discontinue diclofenac and started oral prednisolone (35 mg/day), loratadin tablet (10 mg/day), hydroxyzine tablet (10 mg/day taken at night), chloramphenicol eye

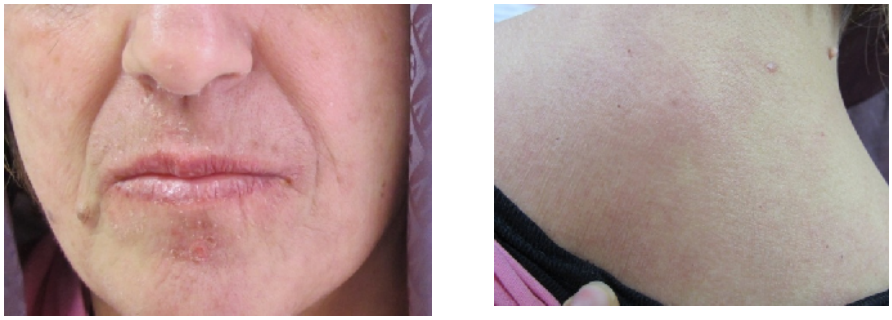

Fig 1. Lesions inpPatient's face and body

drop and eryhthromycin eye ointment. During treatment period, lesions were monitored closely.

The patient was visited by a team of specialists including dermatologist and ophthalmologist.

After 4 days, lesions started to disappear and after 2 weeks, there was no evidence of cutaneous or mucosal ulcers. Result of skin biopsy showed dermo-epidermal separation and a mild dermal lymphocytic infiltration.

DISCUSSION

In 1922, Stevens and Johnson described 2 patients, 7 and 8 years old boys, who had an extraordinary generalized eruption with fever and inflamed buccal mucosa [4,8]. Main differential diagnosis of SJS is toxic epidermal necrolysis (TEN), where its manifestations would be much more severe and over 30% of the skin surface area would be involved [7].

Numerous studies have shown that adverse drug reaction related to hospital admissions are up to 10% of the total number of admissions [9]. SJS is a severe adverse drug reaction characterized by widespread lesions affecting the mouth, eyes, pharynx, larynx, esophagus, skin and genitals. It almost invariably involves the oral mucosa [3,10]. SJS and TEN are frequently associated with drug use [1,4,11]. More than 100 drugs have been associated with the development of SJS/TEN which are reported in single case reports or retrospective studies. Three most common groups of drugs causing these conditions were antimicrobials, NSAIDs, and anti-epileptic drugs [4,12]. In a rare prospective case control study, sulfonamides were the most strongly associated with TEN, followed by antibiotic drugs (in descending order of frequency: cephalosporins, quinolones, aminopenicillins, tetracyclines, macrolides), imidazole antifungals, anticonvulsants (phenobarbital, phenytoin, valproic acid,carbamazepine, and lamotrigine), and then non-steroidal anti-inflammatory drugs (especially piroxicam), allopurinol,and others [3,11]. Among NSAIDs, paracetamol was the most common cause of skin reaction in Indian study [4,12]. But there are very variable reports in different studies. for example, acetaminophen was not a significant risk factor in France [13]. Also Valproic acid, NSAIDs and acetaminophen were significantly associated with these SJS and TEN in children [14].

For overlapping SJS and TEN (when 15 to 30 % body surface area involvement exists), oxicam NSAIDs (piroxicam, meloxicam, tenoxicam) and sulfonamides are most commonly implicated in the United States and other western nations. In contrast allopurinol is the most common offending agent in Southeast Asian nations [15].

Increased use of NSAIDs will increase the number of adverse events related to NSAID use. It has been estimated that 5 to 7 percent of hospital admissions are related to adverse effects of drugs. About 30% of these hospitalizations are related to gastrointestinal, nervous system, renal, or allergic effects of aspirin or non-aspirin NSAIDs [17]. In one study of 373 cases of TEN or SJS and 1720 controls, the oxicam NSAIDs (piroxicam and tenoxicam) had the highest risk (relative risk of 34), while the relative risk with diclofenac and ibuprofen were less (4.1 and 5.3, respectively) [16]. Oxicam derivatives were also suspected in other studies [14,17]. Isoxicam was withdrawn from the market in France after having been associated with 13 cases of toxic epidermal necrolysis [11]. Ibuprofen has been a suspected causative agent of several cases of SJS/TEN including US children [18].

In our case, diclofenac sodium has known as causative agent of SJS because the patient recently started it and with its discontinuing, the symptoms started to relief. Diclofenac sodium (100 mg suppository) was administered twice a day rectally as a back-pain reliever. Topical antiseptics like 0.5% silver nitrate or 0.05% chlorhexidine are usually used for skin lesions to prevent secondary infections [3]. The same treatment was followed in our case. In severe cases, the patient must be transferred to burn units; careful and aseptic handling and sterile field creation must be taken.

Diclofenac is an NSAID and has shown analgesic, anti- inflammatory, and antipyretic activity. Its mode of action is inhibition of cyclooxgenase enzyme. The most common adverse effects of this drug are gasterointestinal problems, like gastritis, peptic ulceration, and abatement of renal function; all of which result primarily from prostaglandin inhibition [19]. Diclofenac-realated skin rash specially sever reactions like SJS is very rare [19]. In litreture review in PubMed and Google Scholar, we found three papers that directly talked about diclofenec and SJS or skin rash [19-21]. Shetty *et al.* reported a 45-year-old female patient that

after dental operation and diclofenac usage as analgesic druge developed SJS [20]. Also, Lin TK *et al.* reported a 78-year-old man who admitted due to a widespread skin eruption after taking NSAIDs drugs (diclofenac, naproxen) [21] . In the last case, Wiwanitkit V presented a diclofenac-related skin rash in a 52 years old female patient [19]. As is apparent, diclofenac-induced skin reactions are common in old ages and our reported case also is 65 year old.

Complications such as thromboembolism and disseminated intravascular coagulation and damage to vital organs such as the kidney function deterioration could occur with use of diclofenac as well, but in our case, no such complications developed [20].

We considered all infectious causes of SJS and after serological test and clinical examination, epidemiologically-prevalent and probable infections in our area (north of Iran) were ruled out in the patient's age group. Several infectious etiologies are implicated in SJS and TEN. Mycoplasma pneumoniae and herpes simplex virus are the most commonly-reported infectious diseases [22]. Viral diseases that have been reported to cause Stevens-Johnson syndrome include the following: Herpes Simplex Virus, Human immunoddeficiency Virus (HIV), Coxsackie viral infections, Influenza, Hepatitis virus and Mumps. Bacterial etiologies include: Group A Beta-hemolytic Streptococci, Diphtheria and 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 [23].

CONCLUSION

SJS is a very rare complication of diclofenac use but due to its dangerous consequences, practitioners should be aware of it and give information to their patients especially if patients are in old ages.

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