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Stevens-Johnson Syndrome as an Unusual Adverse Effect of Azithromycin

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SUMMARY Stevens-Johnson syndrome mostly involves the skin and mucous membranes. The diagnosis is made when the characteristic rash appears 1 to 3 weeks after exposure to a known stimulus and cannot be explained by some other diagnosis. A 62-year-old woman was admitted for evaluation of toxoallergic dermatitis and collagenosis. Ten days prior to admission she was taking a course of azithromycin for upper respiratory tract infection. After a few days she was feeling better but maculopapular, erythematous rash developed over her palms, accompanied by fever and chills as well as reddish discoloration around her eyes. Within the next few days the rash progressed to the feet. Routine hematologic, biochemical and immunologic studies did not confirm the diagnosis of inflammatory rheumatic disease. Corticosteroid therapy with methylprednisolone (1 mg/kg) for the presumed Stevens-Johnson syndrome was started and her condition improved in several days; she became afebrile and her skin lesions gradually disappeared. There is only one report, in a child, documenting the association of Stevens-Johnson syndrome with azithromycin, as in this patient.

KEY WORDS: Stevens-Johnson syndrome, azithromycin

INTRODUCTION

In 1922, Stevens and Johnson (1) described two boys with febrile illnesses associated with cutaneous lesions similar to those of erythema multiforme (EM); they also had stomatitis and severe conjunctivitis that resulted in visual impairment. The disease that they described became known as Stevens-Johnson syndrome (SJS), generally accepted to be a severe form of EM. In 1950, Thomas proposed that SJS be called erythema multiforme major while the mild cutaneous form described by Hebra be called erythema multiforme minor (2). Another syndrome, toxic epidermal necrolysis (TEN), or Lyell's syndrome, in which the epidermis is damaged over large confluent areas

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of the skin surface, and the development of bullae, has also been considered to belong to the erythema multiforme category. The estimated prevalence of TEN is 0.4 to 1.2 cases *per* million population. It was initially described in 1956 by Lyell in four case reports that compared the disease to a scald burn (2). Whether these syndromes, erythema multiforme minor, SJS and TEN, represent a continuum or distinct etiopathologic entities, has not yet been established (3-9). The disagreement focuses on whether the three manifestations (EM, SJS and TEN) are different diseases or variations within the erythema multiforme spectrum (3,7). Descriptive classification focuses on two specific areas: the percentage of complete epidermal detachment from the dermis and the nature of discrete lesions.

The majority of SJS cases are between ages 20 and 40, and 20% of cases occur in children and adolescents (10). The mortality of SJS is reported to be 3% to 19% (11).

SJS is believed to be a cell-mediated hypersensitivity reaction to distinct immunologic stimuli, including infectious agents and drugs (6). The vesiculo-bullous process that is characteristic of SJS is most commonly due to an inflammatory reaction that results in widespread necrosis of keratinocytes. In contrast to other cell-mediated hypersensitivity reactions, the epidermal lymphocytes in SJS are CD8 T cells, which are probably responsible for necrosis of juxtaposed keratinocytes (6). The histology of drug-induced SJS adds more support to the hypothesis of a cell-mediated inflammatory mechanism. The histopathologic observation of “satellite cell necrosis”, which refers to lymphocytes closely associated to pyknotic cells, occurs in both drug-induced SJS and acute graft-*versus*-host disease, the mechanism of which is known to be immunologic and cell-mediated. This makes it likely that the pathogenesis of drug-induced SJS also represents a cell-mediated hypersensitivity reaction.

SJS mostly involves the skin and mucous membranes. Skin lesions are less than 3 cm in diameter, less than 20% of body surface area are involved, with minimal mucous membrane involvement, typically symmetric, and involving the extremities, mostly dorsal and extensor aspects of the hands. The lesions may be erythematous papules, vesicles, bullae, or iris lesions with the additional involvement of at least two mucous membranes, and fever. The appearance of the mucosal lesion is erythema and edema, which progress to erosions and pseudomembrane formation. Prodromal symptoms such as fever, malaise and cough are sometimes reported as a feature, and they usually occur seven to ten days prior to full-blown presentation. Mucosal lesions include conjunctivitis as well as oral and genital ulcers (12-14). The most common and serious long-term SJS sequels are ocular complications. The conjunctivitis causes damage or complete destruction of goblet cells of the conjunctiva, which results in instability of the precorneal tear film, and corneal drying and opacification. The corneal damage can lead to decreased visual acuity and even blindness. The incidence of long-term ocular complications of SJS has been reported to range from 10% to 27% of patients. In addition, hepatitis, nephritis, gastrointestinal bleeding, pneumonia, arthritis, arthralgia, fever, and myalgia have all been reported (15).

The diagnosis is made when the characteristic rash appears 1 to 3 weeks after exposure to a known stimulus and cannot be explained by some other diagnosis (4). The precipitating factors are divided into medications and infectious processes (15,16). The treatment in part depends on the suspected precipitating cause. The implicated drugs such as sulfa drugs, penicillin, or anticonvulsants, especially phenytoin, should be discontinued. The most commonly associated infections are herpes simplex and *Mycoplasma* (17), but there are case reports of a variety of other infective agents (18). There is a substantial body of literature documenting the association of SJS with certain drugs. Much of this literature consists of case reports; however, there are several case series. The drug class most frequently reported to cause SJS are sulfonamides, especially long-acting agents. There also are reports of SJS recurring with subsequent readministration of a sulfonamide. Sulfonamide-induced SJS generally appears one to two weeks of drug therapy initiation. Diphenylhydantoin and penicillin and its derivatives have also been strongly implicated in SJS. As with the sulfonamides, SJS appears 1 to 2 weeks of drug therapy initiation (5,15). There is only one report documenting the association of SJS with azithromycin (19), as in our case.

CASE REPORT

In August 2001, a 62-year-old woman was referred to Department of Nephrology for evaluation of toxoallergic dermatitis and collagenosis. Ten days prior to referral her family physician had prescribed a 1-week course of azithromycin (250 mg *per* day) for the treatment of upper respiratory

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tract infection. After the patient had been taking the medication for four days, she was feeling better but maculopapular, erythematous rash developed over her palms accompanied by fever and chills as well as reddish discoloration around her eyes. Within the next few days, the rash progressed to the feet. She stopped taking azythromycin and was seen at emergency department of another hospital where she was treated with antihistaminics for contact dermatitis and suspect Reiter syndrome. Due to worsening of her condition (fever with large confluent skin areas), the patient was transferred to our hospital on day 10 of the symptom onset.

Her past medical history disclosed polyarthralgia within the last ten years, with sporadic swelling of peripheral joints diagnosed as chronic cervicobrachial and lumbosacral syndrome, and bilateral carpal tunnel syndrome treated mostly by physical therapy and nonsteroidal anti-inflammatory drugs (NSAIDs). A year before, she underwent thorough immunologic check-up because of worsening of polyarthralgia. All laboratory tests including antinuclear antibody and rheumatoid factor were within the normal range, making the diagnosis of inflammatory rheumatic disease and collagenosis less likely. Routine culture of her throat swab was positive for beta hemolytic *Streptoccocus* group A and she was treated with penicillin. Approximately three months prior to admission, she was treated with antimicrobial agents for acute bacterial infection of her lower urinary tract on two occasions. The patient's family history was unremarkable. At the time of admission she was not taking any medications, except for antihistaminics (Synopen i.v., Dimidril 3x1 tbl).

On admission, physical examination revealed a well-developed 62-year-old female. Her vital sings were as follows: temperature 37.5 ˚C, pulse 72 beats *per* minute, and blood pressure 120/80 mm Hg. Head examination revealed periorbital erythema with bilateral conjunctivitis and oral ulcers. On her both hands, predominately palms, the epidermis was separating from the dermis in sheets (Nikolsky's sign) pointing to exfoliative dermatitis. Maculopapulous rash was present on her right knee, and minor circular, erythematous lesions were seen on her feet. There were degenerative malformations of the peripheral hand joints and knees, with reduction of movements in cervical and lumbosacral spine. Otherwise, her physical examination was unremarkable.

Routine hematology and biochemistry studies on admission produced the following findings: elevated ESR (91 mm/h), CRP (62.6 mg/dL) and WBC (12300/mm^3); hematocrit 36%; hemoglobin 125g/L; MCV 89; platelets 255/mm^3; serum iron as low as 7 µmol/L; UIBC 33 µmol/L; serum sodium 138 mEq/L; potassium 4.6 mEq/L; chloride 105 mEq/L; calcium 2.51 mEq/L; blood urea nitrogen (BUN), creatinine, bilirubin and urates were within the normal range; liver enzymes: alkaline phosphatase (AP) 158 U/L; serum glutamic oxaloacetic transaminase (AST) 30 U/L; serum glutamic pyruvic transaminase (ALT) 45 U/L; total serum protein 82 g/L with electrophoresis: albumin 35.8 g/L, α1 globulin 3.6 g/L, α2 globulin 11.1 g/L, β globulin 10.6 g/L, γ globulin 20.8 g/L.

The urine was clear and amber in color, with acidic pH and specific weight of 1.015 g/mL. Microscopic examination showed 0-1 leukocyte. Total protein excretion in urine was 0.05 g/24 h (daily urinary output 0.8 L). Urine cytology revealed rare red blood cells, a few granulocytes, and few squamous and transitional epithelial cells. Her throat swab culture was positive for *Staphylococcus aureus*, while sputum microbiology pointed to *Candida albicans*. Antistreptococcal antibody titer (ASOT) increased to 320 IU/mL. Coagulation study was normal.

Autoimmune serology for serologic markers revealed negative antinuclear antibody (ANA) test, while anti-dsDNA and ENA were not performed. The diagnosis of inflammatory rheumatic disease could not be confirmed. Anti HIV was negative. There was no clinical sign of herpes simplex infection. Skin testing using scratch-patch test with azithromycin was not performed.

An ophthalmologist confirmed conjunctivitis and corneal lesions. Dermatologic examination confirmed the diagnosis of SJS. The patient refused to give approval for taking photographs of her skin lesions.

Corticosteroid therapy with methylprednisolone for the presumed SJS was initiated at a dose of 80 mg i.v. (1 mg/kg), along with topical treatment. Her condition improved in several days, she became afebrile, and her skin lesions gradually disappeared. Skin lesions were treated symptomatically, with analgesics, antipruritics, and local care to lips and gums. Crusted skin lesions were kept moist.

The patient was discharged after 17-day hospital stay, to continue with extensive corticosteroid therapy at a dose of 60 mg i.v. at home, then after 14 days with 40 mg oral corticosteroid, slowly tapering the dose. Other treatments included fluconazole 200 mg i.v. for 10 days and 1 600 000 IU of

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intramuscular penicillin once a month, with regular medical follow-up. The steroid was withdrawn after 3 months. The 4-month control biochemistry testing showed normal ESR, CRP and WBC. Control throat swab culture and sputum analysis were sterile. Control ASOT was within the normal range. At 6 months, control ophthalmologist examination showed no corneal damage. ENA was negative.

DISCUSSION

The incidence of severe EM, SJS and TEN cases that require hospitalization is about 3 to 8 *per* million *per* year (20). Medications have been postulated as the most common etiologic factor in erythema multiforme and TEN (5,15). Antibiotics are reported to cause at least 30% to 40% of cases, with sulfonamides, tetracyclines, amoxicillin, and ampicillin being most commonly implicated. NSAIDs and anticonvulsants, especially Tegretol and phenobarbital, have also been reported. There have also been isolated reports of erythema multiforme occurring after some other medications (16).

Patients are often given antibiotics for an infection, and it is difficult to determine whether the antibiotic or the infection is responsible for the disease. Viral upper respiratory infections, *Mycoplasma pneumoniae*, pharyngitis and herpes simplex infection are also reported to cause erythema multiforme (17). The list of other possible etiologies is extensive, and includes systemic lupus erythematosus, histoplasmosis, pregnancy, malignancy, and external-beam radiation. In most series, some cases remain idiopathic. Several authors have postulated an immunologic etiology for erythema multiforme, although none was able to conclusively demonstrate its pathogenesis (21).

Differential diagnosis includes other diseases that can result in cutaneous and mucous membrane lesions; vesiculo-bullous diseases such as pemphigus vulgaris, erosive lichen planus, and varicella zoster may mimic SJS (20). Behcet's and Reiter's syndromes may have ocular and genital lesions that can be confused with those seen in SJS.

It is important to recognize and expeditiously treat SJS in order to reduce the likelihood of complications, which can be serious. The most frequent are those associated with ocular involvement. Keratitis, uveitis, and perforation of the bulb have all been described with resulting permanent visual impairment. Skin damage and sloughing may occur. This predisposes the patient to sepsis as well as fluid and electrolyte imbalance. If there is widespread epidermal necrosis, the diagnosis should be TEN or Lyell's syndrome and the treatment should be similar to that administered to burn patients (20). Pneumonia may occur in up to 30% of patients with SJS; whether this is a complication or a primary infection precipitating SJS, is unclear. There are rare case reports of hepatic damage, renal insufficiency, and hematologic complications (21). In a review of mucosal involvement in 34 SJS patients, stomatitis was present in 100%, ocular involvement in 86%, genital mucosal or urethral involvement in 41%, and involvement of anal mucosa in only 3% of patients (22).

Guillaume *et al.* reviewed 87 cases of TEN and found that 77% were caused by an adverse drug reaction; the remaining cases were thought to be idiopathic (5). The offending drugs in this study included sulfonamides, anticonvulsants and NSAIDs. The prevalence of TEN is higher in patients with HIV disease than in other patients because of the increased use of sulfonamides for opportunistic infections in these patients (23-25). Non-medicamentous causes are extremely uncommon and include bacterial and viral infections, immunizations, graft-*versus*-host reactions, and malignant tumors. Some cases of TEN have no detectable cause.

The most commonly prescribed therapy for SJS are corticosteroids (26). Because SJS is responsive to corticosteroids, and other immunosuppressive drugs have reported efficacy, it is most likely that an immune mechanism is operative in SJS. The most preferred hypothesis is that a cell-mediated hypersensitivity reaction is pathogenic in SJS (26,27). There are several lines of evidence that support this hypothesis. The time of onset of the reaction of one to three weeks after acquisition of infection or drug administration is very consistent with the temporal response of the known cell-mediated hypersensitivity reactions such as graft-*versus*-host disease and contact dermatitis. There is also a predictable recurrence upon re-exposure to the drug, or recrudescence of infection in case of herpes simplex. In addition, if corticosteroids are tapered too rapidly, there is an exacerbation of SJS that can be reversed by increasing the corticosteroid dose (26).

Currently, most authors do not recommend the routine use of systemic steroids in the treatment of erythema multiforme or toxic epidermal necrolysis. There have been no randomized prospective trials, however, some authorities still believe that a short-term pulse of steroids early in the disease course (as in this patient) may be beneficial in selected patients (19,28).

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This is the second report of SJS associated with azithromycin and the first one in adult patient. Azithromycin has a long half-life, which may be related to the higher risk of adverse effects (29). However, the patient had acute pharygitis, which could prompt the development of SJS.

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