

PHARMACOLOGY

STEVENS-JOHNSON SYNDROME INDUCED BY CARBAMAZEPINE

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Abstract: Stevens-Johnson syndrome (SJS) is a mucocutaneous disorder induced by an immune-complex-mediated hypersensitivity reaction. Nearly half of cases are caused by a reaction to drugs or appear during viral infections and malignancies. A very few cases are caused by a bacterial infection (*Streptococcus*) or *Mycoplasma pneumoniae*. Graft versus host disease is another well-established cause, independent of drugs. No specific etiology has been identified in up to half of cases. We report a 54-year-old man with SJS induced by carbamazepine. Reported patient had prodromal symptoms like fever, headache and polyarthralgia, which preceded mucocutaneous lesions by 3 days. Physical examination on admission, revealed asthenic male with a temperature of 37.2°C and generalized dermatitis with positive Nikolsky sign, large erosions of the palms and soles, onychomadesis, numerous oral and vermilion border of the lips erosions. The patient was administered systemic steroidotherapy and carbamazepine dose was gradually decreased and finally replaced with valproic acid and valproate sodium. During the hospitalization, temperature normalized and the skin lesions disappeared after 3 weeks of treatment.

Keywords: Stevens-Johnson syndrome, carbamazepine, symptoms, management.

Stevens-Johnson syndrome (SJS) is a mucocutaneous disorder that was first described in 1922. It occurs predominantly in Caucasian subjects, with a male to female ratio of 2:1. SJS appears in all age groups but is more common in older people, probably because of tendency to use more drugs. Most patients are in the second to fourth decade, however, it has been reported in children as young as 3 months (1). The disorder is more likely to occur in people with AIDS (2). SJS and toxic epidermal necrolysis (TEN) are two forms of the same life-threatening skin disease induced by an immune-complex-mediated hypersensitivity reaction. In SJS, a patient has blistering of mucous membranes, typically in the mouth, eyes, and vagina and widespread small blisters that arise on erythematous or purpuric maculae. There is a similar blistering of mucous membranes, but in addition the entire top layer of the skin (the epidermis) peels off in sheets from large areas of the body in TEN patients (3). Nearly half of cases are caused by a reaction to drugs (sulfonamides, barbiturates, anticonvulsants, salicylates, cytostatics, thiazide diuretics, cocaine) or appear during viral infections and malignancies.

A very few cases are caused by a bacterial infection (*Streptococcus*) or *Mycoplasma pneumoniae*. Graft versus host disease is another well-established cause, independent of drugs. No specific etiology has been identified in up to half of cases (4).

Case report

A 54-year-old man with generalized dermatitis and large erosions localized on the palms and soles was admitted to our department in February 2006. He had a three-day history of fever (up to 38.2°C), headache and polyarthralgia. The oral pain, dysphagia and first skin manifestations appeared two days later. Skin lesions were described as an erythema-edematous patches forming concentric figures and rings, localized symmetrically on the lower and upper limbs and trunk and large serous blisters placed on the palms and soles. Medical history was only remarkable for arterial hypertension, diabetes mellitus type 2 and alcohol induced epilepsy (diagnosed in August 2005). Medications included glimepiride (Diaprel MR-30 mg once daily) and carbamazepine (Tegretol-200 mg twice daily) during the last six and almost two months, respectively. Family

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history was unremarkable. Physical examination during admission, revealed asthenic male with a temperature of 37.2°C and generalized dermatitis with blisters roofs slipping, large erosions of the palms and soles (Fig. 1), onychomadesis (Fig. 2) numerous oral and vermilion border of the lips erosions (Fig. 3). Mucous membranes were dry with no ocular and genital lesions.

Skin biopsy was performed for H&E histological examination (Fig. 4). Laboratory test results were as follows: RBC 3.66 (nl. 4.00-5.50K/CU MM), HGB 11.4 (nl. 12.0-18.0 g/dL), HCT 34.9 (nl. 37.0-54.0%), erythrocyte sedimentation rate (ESR) 11 mm/hour and 29 mm/2h, albumins 56.6 (nl. 58.8-69.6%), alpha₁ globulins 8.1 (nl. 1.8-3.8%), beta globulins 8.1 (nl. 8.9-13.6%).

The patient was administered prednisone (Encorton - 40 mg once daily), omeprazole (Polprazol - 20 mg once daily), loratadine (Loratan - 10 mg once daily), dexamethasone and neomycin sulfate (Dexapocort N aerosol), 1% chloramphenicol (Detreomycin ointment) topically, and 2% natamycin (Pimafucin) mouthwash solution. The carbamazepine dose was gradually decreased and finally replaced with valproic acid and valproate sodium (Depakine Chrono - 300 mg twice daily) after neurologist referral. During the hospitalization, temperature normalized and the skin lesions disappeared after 3 weeks of treatment.

DISCUSSION AND CONCLUSION

Adverse cutaneous reactions to drugs are frequent and affect 2-3% of all hospitalized patients. SJS and TEN are severe life-threatening dermatoses with mortality rate about 30%. Prompt recognition, early diagnosis, withdrawal of triggering drug and correct management might improve the prognosis (5). The most common drugs responsible for SJS are antiepileptics (carbamazepine, lamotrigine, phenobarbital, phenytoin, valproic acid). Carbamazepine causes SJS/TEN in a frequency of about 14 per 100000 users. In some retrospective studies carbamazepine was the commonest anticonvulsant implicated in SJS and TEN (6). Another study revealed that carbamazepine, phenytoin and allopurinol were most associated with the risk of SJS appearance in the oriental population (7). The risk of SJS and TEN is much higher at the beginning of antiepileptic management and 90% of all cases occur in the first 63 days of treatment (8). In this case, mucocutaneous symptoms specific for SJS appeared two month after carbamazepine application what was consistent with previous epidemiological studies.

SJS and TEN are considered as cytotoxic immune reaction leading to destruction of keratinocytes presenting drug related antigens. Drug metabolites such as arene oxides derived from aromatic anticonvulsive drugs bind to cell constituents if they are not quickly detoxified by epoxide hydrolase. Such metabolites act as haptens and render keratinocytes antigenic. A detoxification system defect may be one of the possible causes of skin adverse drug reactions (9). Patients suffering from SJS usually have prodromal symptoms and signs including fever, cough, sore throat, headache, vomiting, myalgia, polyarthralgia, diarrhea and lethargy. These symptoms occur about 1 to 14 days before mucocutaneous lesions appearance (3). The reported patient had prodromal symptoms like fever, headache and polyarthralgia, which preceded mucocutaneous lesions by 3 days. About 90% of patients suffering from SJS or TEN have a mucosal lesions that usually precede cutaneous symptoms. The buccal mucosa, hard and soft palate and vermilion border of the lips are the most often affected. Some cases also involve tracheal, bronchial and gastrointestinal epithelium, but it was not observed in our patient (10). His mucosal and skin lesions appeared simultaneously and were limited to buccal mucosa and vermilion border of the lips. Conjunctival lesions such as hyperemia, painful erosions, inflammation are present in about 85% of SJS and TEN patients (11). Some patients may complain of dysuria and the anogenital region may be involved in pathological process (12). Prompt withdrawal of drug that is suspected to trigger SJS or TEN may decrease mortality and the risk of new mucocutaneous lesions appearance what was observed in our patient (he did not develop any conjunctival and anogenital lesions) (13).

The differential diagnosis of SJS includes TEN, SJS/TEN overlap, autoimmune blister diseases (pemphigus vulgaris and bullous pemphigoid) and Dühring disease. In SJS erosions or blisters involve less than 10% of the body surface covered with atypical target lesions and maculae (mainly on the trunk). The hemorrhagic-erosive lesions are present on at least one mucosal surface. SJS/TEN overlap is characterized by widespread atypical target lesions and maculae. The erosions or blisters involve 10-30% of the body surface. In TEN syndrome body surface is covered with erosions or blisters in more than 30% and the widespread target lesions and maculae are present. Pemphigus vulgaris and bullous Pemphigoid maybe both present with oral blisters and erythematous skin lesions. The clinical course and the histologic and immunofluores-

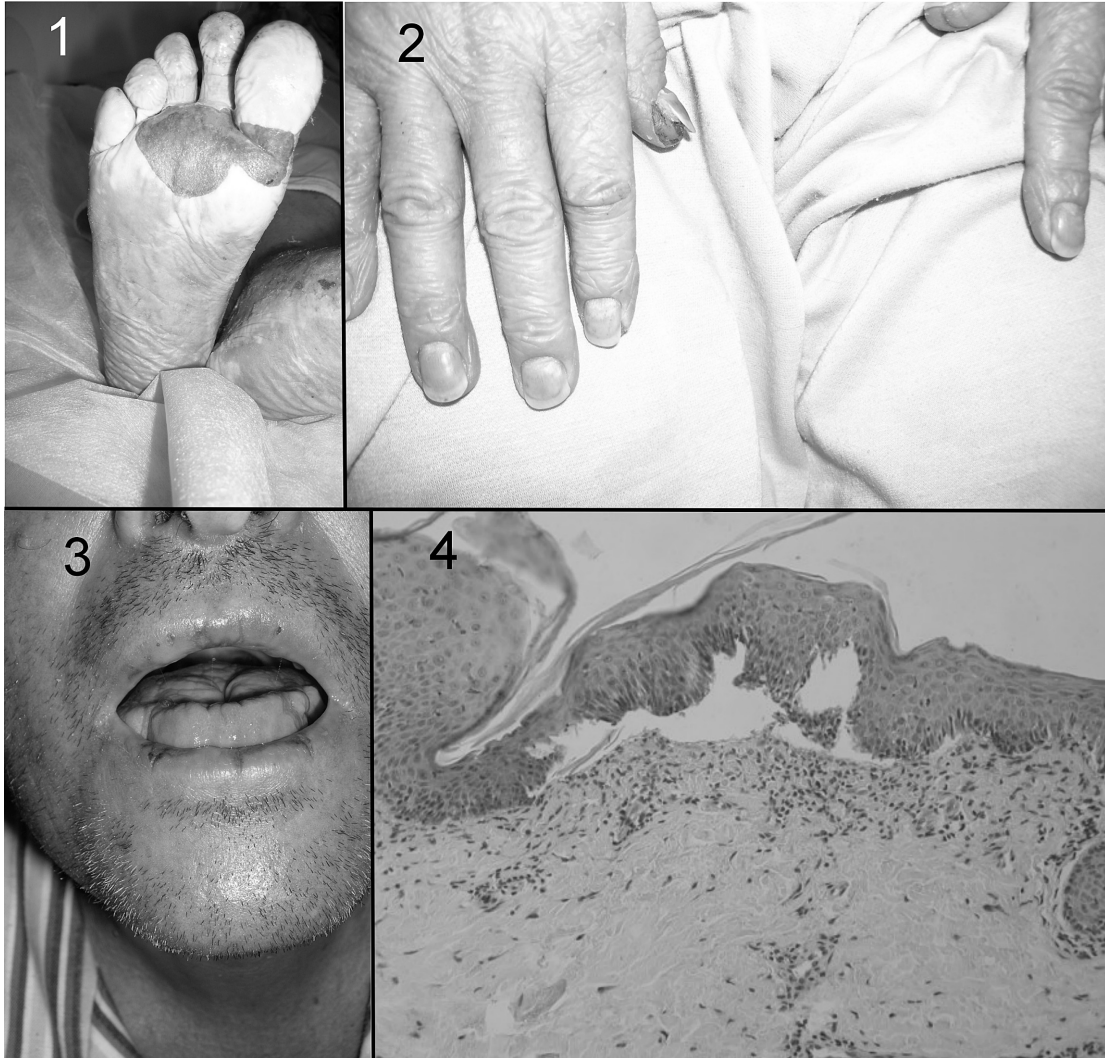


Figure 1. Large erosion localized on the sole.

Figure 2. Thumb onychomadesis.

Figure 3. Hemorrhagic crusts on the lips.

Figure 4. Histological examination (H&E, x200).

Little lymphocytic infiltrate in the upper dermis and a fairly pronounced perivascular infiltrate composed largely of mononuclear cells. The upper dermis shows marked edema resulting in subepidermal blisters and vasodilatation.

cent evaluation produce the answer. The immunopathological differences between autoimmune blister diseases and SJS syndrome concern deposits of immunoglobulins and complement. In pemphigus deposits are located in intercellular spaces of epidermis, in Pemphigoid in epidermal-dermal junction and in SJS only in mucosal vessels. The deposits consist of IgG and C3 in autoimmune blister diseases and IgM and C3 in SJS. Dermatitis herpetiformis very rarely has acral and oral involvement (14).

Systemic corticosteroids were applied (prednisone given orally) after clinical and histological

diagnosis were confirmed in this case. Corticosteroid management is highly debated. They may increase the risk of sepsis (primarily due to *Staphylococcus aureus*, *Pseudomonas spp.*, Gram-negative bacilli or candida) and delay healing (15). On the other hand, some studies reported that early treatment with high doses of systemic steroids ensured a more rapid recovery, mainly in SJS patients where the skin destruction was not too extensive and could be reversed by anti-inflammatory effects of steroids (16). Some studies revealed good therapeutic effect after treatment of SJS patients with systemic steroids simultaneously with

intravenous immunoglobulin therapy (IVIG) and IVIG alone, however, no randomized clinical trial was published. Other authors have not obtained similar results, so rational evaluation of the treatment benefit can not currently be done (17). Our patient did not receive prophylactic systemic antibiotics because they may increase both the emergence of resistant bacteria and the risk of candida sepsis. Antibiotics applied topically (neomycin sulfate and chloramphenicol) were sufficient to avoid bacterial contamination of the erosions and good wound healing. No standard exists about topical treatment of SJS patients. Possible management may be conservative or surgical. The best treatment results were obtained by authors leaving in place the involved "detachable" epidermis and using conservative methods such as topical antiseptics (0.5% silver nitrate or 0.05% chlorhexidine). Good results were also obtained with biologic skin covers after stripping (cadaveric grafts, cultured allogenic or autologous epidermal sheets) or new biological dressings (Apligraf, Biobrane, TransCyte) and after application of recombinant bovine bFGF or recombinant human EGF (18,19).

Carbamazepine is a drug applied not only to patients suffering from epilepsy, but also for pain management, so the number of subjects taking it is increasing. It is very difficult to predict the risk of SJS or TEN appearance in every treated person, but some authors suggest that genetic searching for HLA-B*1502 and patch tests (1% and 10% carbamazepine in petrolatum) could detect high risk patients of SJS or TEN development (20,21).

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