



## Stevens-Johnson syndrome and associated severe mucositis

### Ciężkie zapalenie jamy ustnej związane z zespołem Stevensa-Johnsona

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#### Abstract

The aim of the paper is to present and compare the clinical manifestations and results of treating two cases of Stevens-Johnson syndrome (SJS) and associated mucositis as well as highlighting their most typical clinical features. SJS is the most serious cutaneous adverse drug reaction, usually including oral and ocular involvement, and there is a group of medicines that can cause SJS. Severe mucositis is usually preceded by a painful generalized erythematous vesiculobullous rash and mucosal involvement may extend to the oropharynx, larynx, nasal cavity and respiratory tract. Our cases demonstrated typical lesion development and progression. Mucositis may restrict mouth opening and cause difficulty with eating and speaking. SJS can cause severe, generalized inflammation and multi-organ failure and is characterized by painful mucosal erythema with subsequent blistering and ulceration. In the cases presented here corticosteroids, antihistamines, anti-viral drugs, antibiotics and antifungal drugs were applied.

**Keywords:** Stevens-Johnson syndrome, mucositis, adverse drug reactions.

#### Streszczenie

Celem pracy było przedstawienie i porównanie obrazu klinicznego i wyników leczenia dwóch przypadków zespołu Stevensa-Johnsona i związanego z nim zapalenia jamy ustnej oraz wskazanie ich najbardziej typowych cech klinicznych. Zespół Stevensa-Johnsona jest najpoważniejszym, skórny niepożądanym efektem na leki i zwykle obejmuje reakcje na oku i błonie śluzowej jamy ustnej. Jest grupa leków, które mogą powodować zespół Stevensa-Johnsona. Zapalenie jamy ustnej zwykle poprzedza wystąpienie bolesnej, uogólnionej wysypki pęcherzykowo-rumieniowej. Może rozprzestrzenić się na gardło, krtań, jamę nosową i układ oddechowy. Może ograniczać otwieranie ust i powodować problemy z mówieniem i jedzeniem. SJS może powodować ciężkie, uogólnione zapalenie i uszkodzenia wielonarządowe. Charakteryzuje się bolesnym rumieniem z tworzeniem pęcherzy i owrzodzeń. W leczeniu zastosowano kortykosterydy.

**Słowa kluczowe:** zespół Stevensa-Johnsona, zapalenie jamy ustnej, niepożądane reakcje na leki.

#### Epidemiology

Stevens-Johnson syndrome (SJS) is the most serious and life-threatening cutaneous adverse drug reaction (ADR). The spectrum of diseases that are defined by SJS, the more severe toxic epidermal necrolysis (TEN), and the intermediate (SJS/TEN overlap) are characterized by a severe immunologic dermatobullous condition with high mortality and significant long-term morbidity [1, 2]. The estimated annual incidence of SJS/TEN ranges from 0.4 to 7 cases per million people [1]. SJS/TEN mortality ranges from 1–5% for SJS and 25–40% for TEN. This is characterized by widespread keratinocyte death resulting in extensive epidermal loss with mucous membrane erosions and impaired general condition [3, 4]. The diagnosis of SJS/TEN is made following recognition of the defining clinical

signs and a skin biopsy demonstrating full-thickness necrosis of the epidermis and keratinocyte apoptosis, with minimal involvement of the underlying dermis [1]. SJS and TEN are part of a single disease spectrum that differ only in severity. SJS involves epidermal detachment of less than 10% of the body surface area (BSA), while TEN involves more than 30%. Cases with skin involvement ranging between 10% and 30% are classified as SJS/TEN overlap [5].

#### Aim

The aim of the paper is to present and compare the clinical manifestations and results of treating two cases of SJS and associated mucositis and to mark their most typical clinical features.

### Presentation of cases

In the paper, clinical data from 2 men aged 15 and 24 years affected by SJS are used. The patients were admitted to the Department of Otolaryngology at the District Hospital in Skarżysko-Kamienna as emergency cases. The reason for admission was severe mucositis. In the 15-year-old patient swelling of the upper lip had appeared one week previously. The patient was treated by a general practitioner with antihistamines (Bilastinum) and antibiotics (Amoxicillin). Severe mucositis and painful swallowing were the predominant symptoms. The erythrocyte sedimentation rate rose to 105 mm/h and then decreased to 9. The C-reactive protein level increased to 24.14 and after treatment decreased to 1.3. A chest X-ray and complete blood count did not reveal any findings and no allergies or systemic diseases were determined. For the treatment antiviral drugs (acyclovir), steroids (dexamethasone), antifungals (fluconazole), and antibiotics (cefuroxime) were used. The patient was referred to ambulatory treatment in a stable condition and treatment for bacterial colonizations continued in the Department of Oral Surgery at Poznan University of Medical Sciences. Antiseptic oral rinses were applied twice daily to reduce bacterial colonizations of the mucosa. Additionally, anti-inflammatory oral rinses with benzydamine hydrochloride were used for severe oral discomfort. Topical corticosteroids were also applied to

reduce oral inflammation. Following treatment, the patient's condition was stable without recurrences (**Figure 1**).

The 24-year-old patient was admitted with severe mucositis and pain in the oral cavity. The patient was treated with antibiotics because of an infection to the upper respiratory tract. The symptoms developed over 13 days with severe mucositis, malaise, painful swallowing and sleeplessness being the predominant symptoms. The patient presented with painful mucosal erythema including subsequent blistering and ulceration. A similar involvement of the vermilion of the lips progressed to haemorrhagic sloughing with the development of dark adherent crusts. Mucosal involvement extended to the oropharynx, larynx and nasal cavity. Additionally, both eyes developed ulcerations. The erythrocyte sedimentation rate was 92, 98, 157, 33, 58, and 128 respectively and the C-reactive protein level was 328, 255, 158.3, 89.6, 55.1, 33.99, and 18.21 respectively. A chest X-ray, total protein level and complete blood count did not reveal any findings. The procalcitonin level was not elevated, the HIV-test was negative, and no allergies or systemic diseases were determined. For the treatment steroids (dexamethasone), antifungal drugs (fluconazole), antibiotics (cefuroxime) and antiviral drugs (acyclovir) were used. Follow-up treatment continued at the Department of Oral Surgery (**Figure 2**).



**Figure 1.** Patient 1. Stevens-Johnson syndrome

**Rycina 1.** Pacjent 1. Zespół Stevensa Johnsona



**Figure 2.** Patient 2. Stevens-Johnson syndrome  
**Rycina 2.** Pacjent 2. Zespół Stevensa-Johnsona

### Causes and risk factors

SJS most often represents a reaction to systemic medications. More than 200 offending medications have been implicated as triggers of SJS. The most common causative medications in the aetiology of SJS include allopurinol; antibiotics such as ceftriaxone, cephalosporins, vancomycin, ciprofloxacin, doxycycline, clarithromycin, amoxicillin, and piperacillin-tazobactam; anticonvulsants such as phenytoin, carbamazepine, and lamotrigine; as well as ibuprofen, diltiazem, atenolol, and terbinafine [6]. In the Asian population, carbamazepine, phenytoin, and allopurinol are the most common offending agents [6]. Other reports detail SJS after the ingestion of medicines for the common cold. The symptoms of SJS develop within the first 8 weeks after starting a new medication. There is no evidence that SJS/TEN in response to one class of medication raises the risk for SJS/TEN with a biochemically different class of medications. However, cross-reactivity should be treated as a possible risk factor. SJS has been associated with vaccination and exposure to industrial chemicals and fumes. It has also occurred in patients consuming natural remedies and traditional Chinese herbal medications. Cases of TEN have been reported after radiation therapy and after sun exposure. Several medications e.g. clobazam and phenytoin, and certain viruses, especially HIV, can increase susceptibility to SJS. No more than 70–80% of cases are drug-induced, with SJS, TEN and SJS/TEN overlap all having similar percentages [1, 5]. Bacteria and viruses are also treated as possible causes of SJS. Infection

with *Mycoplasma pneumoniae* is a controversial cause, because it has been associated with erythema multiforme and can cause primary mucositis. Reactivation of herpes simplex also promotes SJS recurrences [1]. In some cases the infection of the upper respiratory tract or therapy with beta-lactam antibiotics might have been a causative or predisposing factor of SJS. In other cases the causes cannot be determined. The idiopathic cases of SJS are more common in children and only a very small percentage of these can be related reliably to infections such as *Mycoplasma pneumoniae*. There is a special form of SJS associated with severe mucositis, a condition known as SJS – *Mycoplasma pneumoniae*-associated mucositis, in which a *Mycoplasma pneumoniae* infection is the main causative factor.

### Clinical presentation

The pattern of clinical signs and symptoms at the onset of SJS varies somewhat among the patients affected, but in general, prodromal fever, malaise and cough are followed by inflammation and ulceration of the ocular, oral and genital mucosa [1]. In our first case, the initial signs of SJS could have imitated the typical symptoms of upper respiratory tract infection. In the second case, swollen lips were the only prodromal symptom of SJS. Swollen lips have not been determined as an initial sign of SJS so far. Severe mucositis usually precedes a painful generalized erythematous vesiculobullous rash. Widespread necrosis involving the skin surface occurs in most patients, with a gradual

onset over a period of 2–15 days. The involvement of the mucous membranes of the mouth and nose is usually an early feature and leads to erosive and haemorrhagic mucositis. Developed erosive mucous membrane lesions and oral involvement have been observed in 97% and 93% of patients with SJS [1]. This is characterized by painful mucosal erythema with subsequent blistering and ulceration. Similar involvement of the vermilion of the lips progresses to haemorrhagic sloughing with the development of dark adherent crusts. The tongue and palate are frequently affected, while in severe cases, mucosal involvement may extend to the oropharynx, larynx, nasal cavity and respiratory tract. Our cases demonstrated typical lesion development and progression. Mucositis may restrict mouth opening and cause difficulty with eating or speaking. A possible long-term complication of acute oral involvement is labial and intraoral scarring as well as sicca syndrome, caused by damage to the minor salivary glands. Xerostomia can develop as a problem in up to 40% of patients. Respiratory tract epithelial necrosis can also occur, resulting in bronchial obstruction and ventilatory compromise. Pulmonary complications are a marker of disease severity and mortality. They do not seem to correlate with the extent of epidermal detachment. Patients with the respiratory involvement of SJS without hypoxaemia suffer no pulmonary complications and usually have low mortality.

SJS/TEN can be associated with the instability of the major body systems. Patients affected may develop severe inflammation of internal mucosal surfaces, including the gastrointestinal and respiratory tracts. Anaemia and lymphopenia are common, but neutropenia is a particularly poor prognostic sign. Serious pulmonary disease may be present even without obvious radiographic abnormalities [1]. Usually, patients with SJS require medical support as well as comprehensive diagnosis and treatment [7]. In our cases physical examination revealed symptoms of general inflammation without symptoms of multi-organ failure and major metabolic abnormalities.

Ocular involvement in the acute phase of the disease has been reported to be between 60% and 100% in adult patients. In survivors, the involvement of the ocular surface with chronic inflammation, desiccation and scarring leading to blindness is the most feared and most significant sequelae of SJS/TEN, with 20–79% of survivors experiencing chronic ocular disease [4]. Among the complications related to SJS or TEN, ocular sequelae were the most common and required prolonged medical care [8, 9].

The differential diagnosis of SJS consists of generalized bullous fixed drug eruption, acute generalized exanthematous pustulosis, erythema multiforme major, burns, acute graft versus host disease, paraneoplastic pemphigus, linear IgA bullous disease, and staphylococcal scaled skin syndrome [1, 5]. Erythema multiforme major (EMM) is often confused with SJS. EMM is typically caused by infection, most commonly herpes simplex virus. It most commonly presents with a minimal degree of mucosal involvement and is characterized by an epidermal detachment of < 10% BSA, coupled with localized typical target lesions or raised atypical targets [1]. In contrast, SJS is typically associated with drugs, presents with prominent mucositis, and is identified histologically by full thickness epidermal necrosis with minimal underlying dermal inflammation [1].

### Treatment

There is no one recommended treatment of SJS and prognosis improves when the offending agent is discontinued as early as possible. Patients with severe SJS should be treated in a Burns Intensive Care Unit, where necrotic skin is debrided, and exposed areas covered with artificial membranes or biologic dressings which enhance healing and reduce discomfort, scarring and infection [1]. Patients with SJS should be managed by a multidisciplinary team taken from the fields of ophthalmology, dermatology, otolaryngology, oral medicine and pathology, internal medicine, as well as intensive care [9]. Because immunological pathomechanisms are involved, therapeutic interventions include corticosteroids, other immunosuppressants, and agents expected to block soluble cell death mediators or their receptors [3]. There is currently insufficient evidence to recommend systemic corticosteroids for the treatment of the oral manifestations of acute SJS. However, steroids are commonly used in a variety of doses for 5–7 days during acute illness, though in paediatric patients systemic corticosteroids significantly increase the rate of severe complications. Moreover, the evidence for the use of systemic corticosteroids for SJS in adults is inconsistent. However, in our two cases corticosteroids reduced the severity of later complications and were effective and well-tolerated. Corticosteroids dampen the immune response to exogenous agents [1], and high-dose pulsed steroids administered in the earliest stages of disease may limit progression. Usually, oral assessment reveals the complete remission of lesions 7–10 days after the start of systemic corticosteroid treatment. Alternative treatment includes human intravenous immune globulin, plasmapheresis,

granulocyte colony stimulating factor, cyclosporine, cyclophosphamide and TNF-alpha inhibitors. Plasmapheresis is safe with minimal complications but human intravenous immune globulin can give rise to acute renal failure [1]. Local surgical management may include debridement of pseudomembranes, amniotic and mucous membrane grafting, as well as reconstructive procedures [9]. Additionally, regular local emollients, topical analgesics and antiseptics are recommended for oral SJS. Topical corticosteroids are prescribed for oral SJS as they reduce oral inflammation. During mucositis, oral and lip swabs should be taken regularly if bacterial infection is suspected. The slow healing of oral mucosa may reflect secondary infection by, or the reactivation of, HSV. Diluting a 0.2% chlorhexidine mouthwash by up to 50% will reduce the soreness that can accompany this treatment. Topical corticosteroids (Orabase, betamethasone sodium) can be applied four times daily during the acute phase [10].

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