

Stevens-Johnson syndrome and herpes simplex reactivation associated with paracetamol use. Case report

Síndrome de Stevens-Johnson con reactivación de herpes simple asociado a la ingesta de paracetamol. Reporte de caso

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Abstract

Introduction: Stevens-Johnson syndrome (SJS) is a rare disease that affects the skin, as well as the oral, ocular, and urogenital mucous membranes. This condition is caused by drug reactions in more than 50% of cases.

Case presentation: A 20-year-old male visited the emergency service of a tertiary care hospital of Popayán due to a 10-day history of asthenia, adynamia, fever (without objective measurement records), cough with scarce whitish sputum, and headache that improved with paracetamol treatment. However, his condition worsened in the last two days, and he developed hyporexia, pharyngeal pruritus, vesicles, and blisters on the corners of the mouth, the oral mucosa, the trunk, and limbs, as well as breathing difficulty and odynophagia, prompting him to seek medical treatment at the ER. At first, disseminated herpes simplex, systemic lupus erythematosus and SJS were suspected, but based on clinical and laboratory findings, the patient was finally diagnosed with SJS with herpes simplex reactivation associated with the use paracetamol. Consequently, the administration of this drug was stopped and management with acyclovir and methylprednisolone was started. The patient progressed satisfactorily and was discharged 10 days after beginning the new treatment, and his general condition was optimal during follow-up appointments.

Conclusion: The occurrence of SJS may be associated with the oral administration of paracetamol; nevertheless, its use is not discouraged due to its great overall benefits. In this sense, given that paracetamol is an over-the-counter drug widely used in Colombia, recognizing the clinical manifestations of SJS is essential to provide adequate management and avoid complications in cases such as the one reported here.

Keywords: Stevens-Johnson Syndrome; Herpes Simplex; Acetaminophen; Erythema Multiforme; Drug Eruptions; Colombia (MeSH).

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Resumen

Introducción. El síndrome de Stevens-Johnson (SJS) es una enfermedad poco común que afecta la piel y las mucosas oral, ocular y urogenital; además, en más del 50% de los casos es producida por reacciones a medicamentos.

Presentación del caso. Hombre de 20 años quien asistió al servicio de urgencias de un hospital de tercer nivel de Popayán (Colombia) por un cuadro clínico de 10 días de evolución consistente en astenia, adinamia, fiebre no cuantificada, tos con escasa expectoración blanquecina y cefalea, sintomatología que mejoraba con el uso de paracetamol; sin embargo, la condición del paciente empeoró en los últimos dos días, presentando hiporexia, prurito en faringe, vesículas y ampollas en comisuras labiales, mucosa oral, tronco y extremidades, además de dificultad respiratoria y odinofagia, razón por la cual acudió al servicio. En principio se sospechó de herpes simple diseminado, lupus eritematoso sistémico, y SJS; sin embargo, con base en los hallazgos clínicos y de laboratorio se confirmó el diagnóstico de SJS con reactivación de herpes simple asociado a la ingesta de paracetamol, por lo que se suspendió este medicamento y se inició manejo con aciclovir y metilprednisolona. El paciente tuvo una evolución satisfactoria y fue dado de alta a los 10 días del inicio del nuevo tratamiento y en las citas de control su condición general era óptima.

Conclusiones. El desarrollo de SJS puede estar asociado al consumo de paracetamol; sin embargo, su uso no se desaconseja gracias a sus grandes bondades y beneficios generales. En este sentido, dado que el paracetamol es un medicamento de venta libre y uso extenso en Colombia, es indispensable reconocer las manifestaciones clínicas del SJS para poder dar un manejo adecuado y evitar complicaciones en casos como el aquí reportado.

Palabras clave: Síndrome de Stevens-Johnson; Herpes simple; Acetaminofén; Eritema multiforme; Erupciones por medicamentos; Colombia (DeCS).

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Introduction

Stevens-Johnson syndrome (SJS) is a disorder that causes oral, ocular, and genital mucocutaneous rash,¹ with an annual incidence of 1.2–6 cases per million inhabitants, with women being more affected than men (1.5:1).² Patients with SJS have epidermal desquamation on less than 10% of their body surface, and, in some cases, desquamation may occur as a secondary lesion at the end of the disease process. It is essential to keep in mind that when lesions are present in 10–30% of the skin, there is an overlap between SJS and toxic epidermal necrolysis (TEN), but when this percentage exceeds >30%, it is considered to be TEN (also known as Lyell's syndrome), a potentially life-threatening condition.

Mortality from SJS depends on the time of reaction onset, the extent of epidermal detachment, the patient's age, and underlying conditions. From the least to the most severe degree of skin involvement, mortality is almost 10% for patients with SJS, approximately 30% for patients with SJS/TEN overlap, and almost 50% for patients with TEN.³ It should be noted that SJS and TEN are considered two clinical spectrums of the same disease.⁴

At present, the etiopathogenesis of SJS has not been fully elucidated, although it has been associated with malignancies (leukemia, lymphomas), autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, Hashimoto's disease, and sarcoidosis), drug reactions, and genetic (HLA antigen alleles), immune and infectious factors (herpes simplex virus (HSV) 1 and 2, herpes zoster, Epstein-Barr virus, cytomegalovirus, herpesvirus 6, 7 and 8, HIV, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Mycobacterium tuberculosis* and *Candida spp.*)^{5–12}

SJS may be defined based on the involvement of two or more mucous membranes or calculating the percentage of body surface area affected. When symptoms appear, erythematous macules, which turn purplish-red and then

grayish, are seen; flaccid and painful blisters eventually form, predominantly on the face and trunk. The so-called "target lesions" or "iris lesions" are observed in SJS, which can have three presentations: (i) typical raised target lesion (two concentric erythematous rings or circles over a central zone), (ii) atypical raised target lesion (a single raised, concentric erythematous ring or circle over a central point), and (iii) flat atypical target lesion (one or two flat concentric erythematous rings or circles over a central point).¹³ If symptoms progress to TEN, the Nikolsky's sign can be recognized, in which the epidermis is detached from the deeper layers of the skin when massaging or rubbing the skin.¹²

The following is the case of a patient who developed SJS with reactivation of herpes simplex following paracetamol ingestion.

Case presentation

A 20-year-old patient attended the emergency department of a tertiary care center in Popayán due to a 10-day history of asthenia, adynamia, unquantified fever predominantly in the afternoon, episodes of cough with scanty whitish sputum, and episodic tension headache in the frontal region with intensity of 6/10 on the analogue scale of pain for 10 days; the symptoms improved after taking 1g of paracetamol, which the patient self-medicated on the fifth day of symptom onset.

On the eighth day, the patient presented vesicles in the corners of the mouth of 1–2 mm in diameter, and the next day he developed a sensation of pruritus in the pharynx and hyporexia, as well as vesicles and blisters accompanied by pruritus in the oral mucosa, forearms, trunk, and limbs. On the tenth day, he presented with an episode of odynophagia and respiratory distress, so he decided to visit the emergency department, where he was hospitalized (Figure 1).

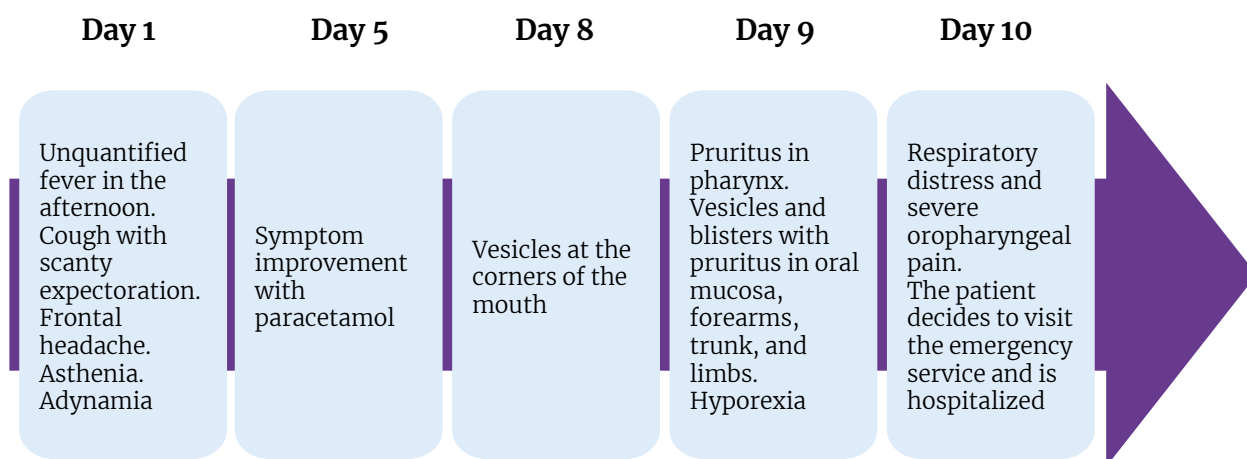


Figure 1. Timeline of clinical manifestations prior to consultation. Source: Own elaboration.

His personal medical history included chickenpox and measles during childhood; two episodes of oral herpes in the last seven years, which were satisfactorily treated with topical acyclovir; and allergy to apitoxin and soaps

with salicylic acid and glycolic acid in their composition. In addition, the patient denied the use of drugs other than paracetamol and stated that he had a stable heterosexual partner and used barrier methods as a contraceptive method.

Upon physical examination on admission, he had the following vital signs: heart rate of 106 bpm, blood pressure of 130/70 mmHg, respiratory rate of 22 rpm, temperature of 36.5°C, and blood glucose of 135 mg/dL. Erythema and epiphora were also evident in both eyes, as well as extensive erosion in oral and nasal mucosa with erythema, hemorrhagic crusts in the vermilion zone,

sialorrhea (Figure 2), and multiple vesicles and blisters in the thoraco-abdominal region and limbs along the dermatomes, of which some had a dark violaceous or hypochromic center and erythematous halo (Figure 3). The genital examination showed erosion of the glans and foreskin. No further alterations were found during the examination.



Figure 2. Extensive erosion of oral and nasal mucosa.
Source: Documents obtained during the study.



Figure 3. Vesicles and blisters on dorsum and left arm.
Source: Documents obtained during the study.

The initial diagnostic impression was disseminated herpes simplex with possible immune involvement, so it was decided to hospitalize the patient and perform a chest X-ray that showed no alterations, in addition to a blood count that reported normal electrolyte levels, leukocytosis with

neutrophilia, and elevated serum creatinine, blood urea nitrogen and C-reactive protein (CRP) levels. Laboratory tests were also requested, including a rapid test for HIV 1 and 2, serological test for syphilis, and hepatitis B test (Table 1). A dermatology assessment was also performed.

Table 1. Laboratory test findings.

Test		1st day of hospitalization	5th day of hospitalization
Blood test	Total leukocyte count	14.1x10 ³ /uL	8.3x10 ³ /uL
	Neutrophils	9.8x10 ³ /uL	6.5x10 ³ /uL
	Lymphocytes	1.8x10 ³ /uL	1.0x10 ³ /uL
	Lymphocytes	17.2 g/dL	14.9 g/dL
	Hematocrit	51.3%	44%
	Platelets	389x10 ³ /uL	310x10 ³ /uL
Kidney function	Serum creatinine	1.5 mg/dL	0.8 mg/dL
	Blood urea nitrogen	25 mg/dL	14 mg/dL
Liver function	Aspartate aminotransferase (ASAT-TGO)	50 U/L	22 U/L
	Alanine aminotransferase (ALAT-TGP)	90 U/L	75 U/L
	Alkaline phosphatase	137 U/L	108 U/L
	Lactate dehydrogenase	159 U/L	128 U/L
	Total bilirubin	1.7 mg/dL	0.5 mg/dL
	Direct bilirubin	0.5 mg/dL	0.1 mg/dL
	Indirect bilirubin	1.2 mg/dL	0.4 mg/dL
	C-reactive protein	31.3 mg/dL	9.3 mg/dL

Source: Own elaboration.

Initial treatment consisted of maintenance intravenous fluids, prophylactic antibiotics (ampicillin sulbactam 3g IV every 6 hours), fluconazole 200mg IV every 24 hours for prophylaxis of opportunistic infections, acyclovir 500mg IV every 8 hours, analgesics (tramadol 25mg IV every 6 hours, and dipyrrone 1g IV every 8 hours), and ranitidine 50mg IV every 8 hours for gastric protection. Mouth rinses with nystatin 10mL every 6 hours were also prescribed.

On the second day of hospitalization, the patient was assessed by the dermatology service once again, establishing a differential diagnosis between SJS and systemic lupus erythematosus (SLE). Consequently, a skin biopsy and the following tests were requested: antinuclear antibodies, anti-DNA antibodies, C3 and C4 proteins, lupus anticoagulant, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), antineutrophil cytoplasmic antibodies (c-ANCA), and anti-cardiolipin antibodies. Immunological profile was negative, and HIV, syphilis and hepatitis B were ruled out.

Based on the findings, paracetamol and prophylactic antibiotic and antifungal medication were stopped, and the patient was treated with methylprednisolone 50mg IV every 8 hours, artificial tears, and sucralfate suspension 5mL every 6 hours. After five days of hospitalization, control blood, kidney and liver function, and CRP tests were performed, showing improvement compared to the values obtained on the day of admission (Table 1).

The patient had a satisfactory progress and was discharged after 10 days of hospitalization. During subsequent follow-up appointments (at two weeks with the internal medicine service and at two months with the dermatology service), he was found in good general condition, although there was evidence of dyschromic macules in

the thorax without ocular or genital involvement in the last consultation.

Discussion

The diagnosis of SJS is based mainly on clinical findings (fever, involvement of two or more mucous membranes, and <30% involvement of the body surface), with biopsy and histological examination being required for confirmation. It is worth noting that in the case reported here, these parameters were met, but the histopathology photograph could not be included in the report due to administrative complications with the laboratory.

According to the literature,¹⁴ the pathology study in SJS cases reports initial lesions with superficial perivascular lymphocytic infiltrate, together with dermal edema, accumulation of lymphocytes along the dermoepidermal junction, and degenerative and necrotic keratinocytes (interface dermatitis pattern). As the syndrome progresses, lymphocytes ascend to the epidermis and there are confluent, demarcated areas of epidermal necrosis with blister formation leading to epidermal detachment. Macroscopically, the lesion observed is a typical target lesion (blister or area of central epidermal necrosis surrounded by macular erythema), as evidenced in the case reported here (Figures 2 and 3).

Although the patient in the present case only had some dyschromic macules on the thorax as sequelae, in 90% of the cases there are evident ocular complications.^{1,15}

Systemic manifestations in SJS include a discrete elevation of transaminases, altered kidney function test, and intestinal and respiratory symptoms with sphacelation of the epithelium.^{15,16} In the reported case, the liver

profile was slightly elevated, and renal function alteration, leukocytosis with neutrophilia and elevated CRP were determined, all of which were attributable to the systemic inflammatory response. Even though there is usually pulmonary involvement (alveolar lesion) in one third of the cases of this syndrome,¹³ the patient in this case had no respiratory complications and the chest X-ray showed no alterations.

The acute phase of SJS is marked by nonspecific symptoms (fever, myalgias, arthralgias, ocular irritation, odynophagia, and cough) that appear days before the onset of cutaneous manifestations, as was the case of this patient. Furthermore, in more than 90% of cases, erosions appear in the oral, nasal, ocular and/or urogenital mucosa, which in severe cases also involve the respiratory and gastrointestinal mucosa.^{12,16} This patient had lesions on less than 30% of the body surface, which, as noted above, is a characteristic of SJS. Because SJS and TEN can overlap, they are considered to be within the spectrum of the same disease and should not be mistaken for erythema multiforme minor, which is more of an antiherpetic reaction than a drug allergy.¹³

The concomitant infectious component of herpes simplex reactivation as a predisposing factor for SJS is interesting since it has been linked to the family of human herpes viruses by various authors since the 1980s (HSV 1 and 2, varicella zoster, Epstein-Barr virus, cytomegalovirus, and herpesviruses 6, 7 and 8.)¹⁷⁻²² However, according to Irungu *et al*,²³ various analytical epidemiological studies have been conducted since 2015, showing conflicting results and attributing 94.8% of SJS/TEN cases to drug usage and only 5.2% to infectious agents (HIV, HSV 1, and *M. pneumoniae*).

Furthermore, by 2013, the Food and Drugs Administration had already issued a report on the risk of rare but severe skin reactions, such as SJS, TEN, and acute generalized exanthematous pustulosis following paracetamol consumption.²⁴ Other studies have also described the association of SJS with more than 100 drugs (including paracetamol),²⁵⁻²⁸ most notably EuroSCAR, which monitored the risks of SJS/TEN as a drug reaction through case-control studies (Table 2).²⁸ It should be noted that the patient in the present case consumed paracetamol five days before consultation.

Table 2. Drugs with a risk of causing Stevens-Johnson syndrome/toxic epidermal necrolysis.

High risk	Low risk	Potential risk *	Undetermined risk
Nevirapine Lamotrigine Carbamazepine Phenytoin Phenobarbital Sulfonamides Allopurinol Sulfasalazine Nonsteroidal anti-inflammatory drugs (oxicams)	Sertraline Macrolides Quinolones Cephalosporins Tetracyclines Aminopenicillins	Paracetamol Corticosteroids Acetylsalicylic acid Pyrazolones Tramadol Ibuprofen Pantoprazole Nimesulide	Beta-blockers Angiotensin-converting enzyme inhibitors Calcium channel blockers Thiazide diuretics Furosemide Propionic acid Insulin Antidiabetic sulfonylureas Proton pump inhibitors

* Further evidence required.

Source: Own elaboration based on Mockenhaupt *et al*.²⁸

In cases of SJS, laboratory tests are necessary to determine whether there is systemic involvement, and the Score of Toxic Epidermal Necrosis (SCORTEN) test is useful to establish the severity and risk of mortality (Table 3). However, this score does not consider possible concomitant infections and immune involvement, which have

been reported to be predisposing factors in the pathophysiology and natural history of SJS/TEN. After assessing all items, except bicarbonate, the reported patient had a systemic involvement of 3.2%; it is important to mention that arterial blood gas tests were not performed due to an infectious process at the puncture site.

Table 3. Independent prognostic factors in Stevens-Johnson syndrome/toxic epidermal necrolysis: each parameter is assigned 1 point.

Age	≥40 years
Heart rate	≥120 bpm
Diagnosis of malignancy	Yes
Body surface with detachment on the first day of admission	>10%
Blood urea nitrogen	>28 mg/dL
Bicarbonate	<20 mg/dL
Glucose	>252 mg/dL
SCORTEN (mortality rate)	0-1 (3.2%) 2 (12.1%) 3 (35.3%) 4 (58.3%) >5 (90%)

Source: Own elaboration based on Bastuji-Garin *et al*.²⁹

The main differential diagnoses of SJS/TEN are fixed erythema pigmentosum, bullous skin diseases (pemphigoid, erosive lichen planus), SLE (Rowell syndrome), Behcet's disease, linear IgA dermatosis, and staphylococcal scalded skin syndrome.^{12,30,31} It should be noted that, although several authors have reported the association of SLE with SJS/TEN,^{30,32-34} the patient was negative for immunological profile.

The Centers for Disease Control and Prevention state that it is not mandatory to screen for HSV 1 or 2 in the general population; however, one of its indications is to perform serology tests in patients with a clinical diagnosis of active HSV 1 or 2 infection and no confirmatory test.^{35,36} This is mentioned because, due to administrative difficulties with the health care delivery company, it was not possible to request antibody tests, cell culture or Tzanck test, nor was it possible to perform polymerase chain reaction to confirm the concomitance of these viruses with SJS, despite the symptoms being very suggestive.

The limitations of this study include the fact that it was not possible to attach the histopathology image and that, as mentioned above, due to administrative reasons, arterial blood gas tests were not performed, nor were serology, cell culture, Tzanck test or molecular tests for HSV 1 and 2 and other herpesviruses.

Conclusions

The development of SJS may be associated with the consumption of paracetamol; however, its use is not discouraged due to its great overall benefits. In this sense, given that paracetamol is an over-the-counter drug widely used in Colombia and that it is also classified as a potential risk in the EuroSCAR study, it is essential to recognize the clinical manifestations of SJS to provide adequate treatment and avoid complications in cases such as the one reported here.

Ethical considerations

The patient consented the preparation and publication of this case report.

Conflicts of interest

None stated by the authors.

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