

## Drug Hypersensitivity: Stevens Johnson Syndrome in a Teenage Patient

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### Abstract

The Stevens Johnson Syndrome (SJS) is one of the most severe skin diseases, with a high morbidity and mortality. It is part of a spectrum of reactional dermatitis and is distinguished by the extent of affected skin.

The majority of cases are the result of a hypersensitivity reaction to viruses, fungi, bacteria, infections, malignancies, or the ingestion of some medication, the latter being the most common cause.

In the present article we present the case of a male patient of 23 years of age who attends the medical clinic service of the General Interzonal Hospital of Acute President Perón de Avellaneda, presenting a hypersensitivity reaction associated with antiepileptic medication, compatible with Stevens Syndrome Johnson.

**Keywords:** Steven Johnson Syndrome; Hypersensitivity; Medications

### Introduction

According to the WHO, a severe drug reaction is defined as "one that requires hospitalization or prolongation of a pre-existing hospital stay, that causes a persistent or significant disability, that threatens life or causes death." The Stevens Johnson syndrome falls into this category [1,2].

Clinically, it is a muco-cutaneous reaction characterized by a macular eruption on the face and trunk, with the presence of fever in the first days, culminating with the formation of bullae and the presence of the Nikolski sign as a result of a decoupling of the epidermis and dermis [3].

Etiologically, allopurinol and carbamazepine are the most frequent causative agents of SJS, but penicillins and cephalosporins have also been implicated; the causal agents vary according to the prescription trends. More than 100 associated drugs have recently been described, such as non-steroidal anti-inflammatory drugs, sulfonamides, aminopenicillins, antiretrovirals, antiepileptics such as phenytoin, lamotrigine and barbiturates, among others [3,4]. It is considered that there are three pathogenic mechanisms that cause drug reactions by drugs: immunological, non-immunological and idiosyncratic mechanisms [5,6].

The risk of suffering from the Stevens-Johnson Syndrome is greater during the first week of treatment for most medications, and in the case of anticonvulsants, during the first two months [7,8].

Stevens-Johnson syndrome has an annual incidence of 1.2 to 6 cases per 1 million and toxic epidermal necrolysis (TEN), from 0.4 to 1.2 cases per 1 million. The second predominates in women with a ratio of 1.5: 1. Mortality depends mainly on the compromised body surface area and the age of the patients and is estimated to be 5% for Stevens-Johnson Syndrome and 25% to 50% for toxic epidermal necrolysis [9].

### Clinical classification

Taking into account the morphology of the lesions and the compromised areas, we can classify it in [7,10]:

- Stevens-Johnson syndrome: Erythematous or purple-colored macules or non-palpable atypical target lesions that compromise less than 10% of the body surface.
- Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN): Flat atypical target lesions, disseminated purple macules that compromise 10 to 30% of the body surface.
- Toxic Epidermal Necrolysis with purple macules of ill-defined edges spots: Purple maculae, disseminated with poorly defined edges or flat atypical target lesions associated with an epidermal detachment of 30% of the body surface.
- Toxic Epidermal Necrolysis without purple macules of ill-defined spots: Generally, commits the trunk with blisters and large sheets of epidermal detachment of more than 10% of the body surface, without maculae or atypical target lesions that precede them.

### Differential diagnosis

A difficult differential diagnosis is Erythema Multiforme Mayor (EMM), whose clinical presentation can simulate a Steven Johnson Syndrome (SJS) in the early stage. EMM is a self-limited mucocutaneous disease that does not belong to the spectrum of SJS and Toxic Epidermal Necrolysis (TEN). EMM can be caused by medications, but its etiology is mostly an infectious agent [11-13].

Regarding other bullous diseases, it should be differentiated from acute generalized pustulosis (AGEP), which is caused by an adverse reaction to medications and clinically is characterized by multiple non-follicular pustules with predisposition for the corporal folds and the face, and a mucosal involvement of 20%. In histopathology, the presence of a subcorneal pustule with an intraepidermal neutrophilic infiltrate without epidermal detachment is observed.

The scalded skin syndrome occurs in adult patients with kidney damage or immunosuppression states. It is caused by *Staphylococcus aureus* exotoxin that is directed against desmoglein 1, with the subsequent formation of flaccid subcorneal blisters with epidermal defacement. Other diseases are subepidermal blisters are paraneoplastic pemphigus and acute graft-versus-host disease [1,14].

### Clinical Situation

For the publication of the present case fundamentally the rights of the patient were protected, firstly under the consent signed by the grandmother of the represented and the authorization in the area of teaching of the Interzonal General Hospital of Acute President Perón, respecting the ethical principles based on the Declaration of Helsinki.

It is presented in the medical guard of the “Interzonal General Hospital of Acute President Perón de Avellaneda”, epileptic male patient of 23 years of age, accompanied by his grandmother.

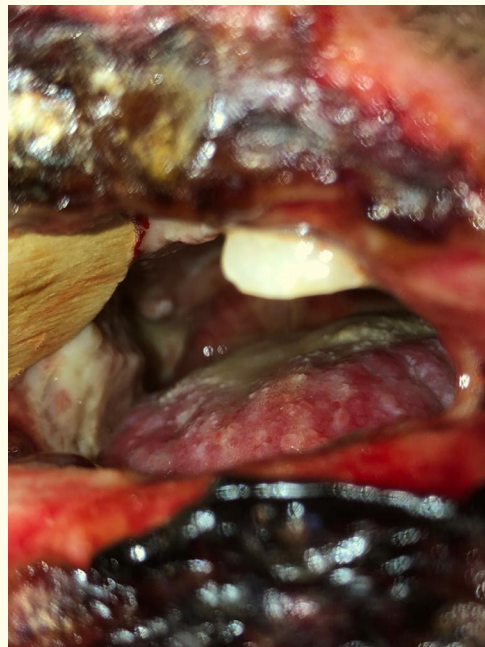
At the time of the consultation, she presented with food, dipsia and decreased diuresis. He refers to being medicated with Carbamazepine, Clobazam and currently a new anticonvulsant, Oxcarbazepine. In addition, the patient’s companion, reports that one week before the time of consultation, the patient presented pain and discomfort at the time of feeding and swallowing.

Upon physical examination, erythematous conjunctivae with serous secretion and diminished mouth opening are observed. The oral cavity is also observed erythematous and with seropurulent secretion (Figure 1a-1c and 2a, 2b).

Intensive treatment is performed with suspension of basic medication. Prophylaxis of mucous membranes with hydrogen peroxide is indicated and continue treatment with Levetiracetam. It is evaluated by the toxicology and infectious diseases service, and specific treatment is indicated.



**Figure 1a**



**Figure 1b**



**Figure 1c**

**Figure 1a-1c:** In these photographs you can see the oral status of the patient at the time of entering the service. Bleeding with exobuccal scabs is observed. Poor oral state, perioral pain, with little opening with the erythematous endobuccal mucosa and with seropurulent secretion.



**Figure 2a**



**Figure 2b**

**Figure 2a and 2b:** Blistering reactions can be observed due to pharmacoderma in the neck area, some of which are bleeding.

Laboratory studies, electrocardiogram (ECG), chest x-ray, renal function, urine cultures, and extended acid-base status are performed.

Hypothetically, the syndrome is produced by drug interaction between Amoxicillin/Clavulanic Acid, and its basic medication.

It also presents on the back, trunk, palms of the hands and soles of the feet, raised lesions, painless on palpation, bullous lesions in the lateral region of the neck and mucositis in the oral cavity (Figure 3-7).



**Figure 3**





Figure 4



Figure 5



Figure 6



**Figure 7**

**Figure 3-7:** Back, trunk, palms and soles of the feet raised lesions, painless on palpation. An intense red dermal reaction can be observed.

In conjunction with the medical evaluation, it was decided to perform the lesional dermal biopsy of one of the blister lesions for confirmation through the pathological anatomy of the syndrome. For this, a representative area of the neck with a bullous lesion of approximately 1.4 cm by 0.9 cm in diameter was evidenced (Figure 8 and 9). Anesthesia was performed far from the bullous lesion so as not to alter the sample of same with cartilaine plus epinephrine. An incision was made below the bullous lesion respecting the muscular plane, the excision was performed and it was sutured. The sample was sent to the pathology department of the Faculty of Dentistry of the University of Buenos Aires. The submitted piece measures 1.4 x 0.9 x 0.4 cm (Figure 10).



**Figure 8:** Anatomical region of the neck where the pathological anatomy sample was taken.



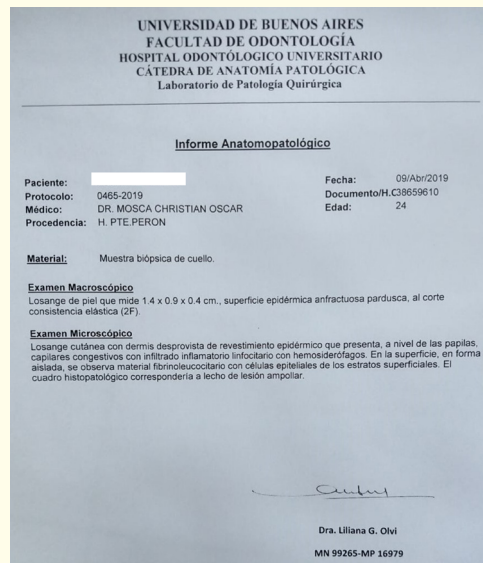
**Figure 9:** Excisional sample with scalpel for referral to the pathology department.



**Figure 10:** Size of the biopsy sample.



The anatomopathological diagnosis revealed a cutaneous anange with a dermis devoid of epidermal lining that presents, at the level of the papilla, congestive capillaries with lymphocytic inflammatory infiltrate with hemosiderophages. On the surface, in isolated form, fibrinoleukocytic material is observed with epithelial cells of the superficial layers. The histopathological picture corresponds to a bed of bullous lesion (Figure 11).



**Figure 11:** Pathological anatomy report with description of the lesion (cutaneous angioma with dermis devoid of epidermal lining that presents, at the level of the papilla, congestive capillaries with lymphocytic inflammatory infiltrate with hemosiderophages). On the surface, in isolated form, it is observed fibrinoleukocytic material with epithelial cells of the superficial layers. The histopathological picture corresponds to bed of bullous lesion).

After one week, an improvement was observed with respect to the mouth opening and mucositis. Therefore, it is decided to suspend the containers with hydrogen peroxide.

The patient is discharged 12 days after admission, continuing the outpatient treatment with Levetiracetam 750 mg every 12 hours; Cream of Fusidic acid plus Betamethasone; Omeprazole 40 mg; Miconazol cream in inguinal and interdigital region; Ophthalmic solution 2 drops every 2 hours with treatment follow-up due to toxicology and neurology.

## Discussion

Stevens-Johnson syndrome and toxic epidermal necrolysis are idiosyncratic reactions, infrequent, affecting patients of any age and race, who consume medications [9]. In association with this we can describe the syndrome of hypersensitivity to anticonvulsants (SHA).

Among anticonvulsants, aromatics are the most commonly involved in these reactions. Taking into account the classification of aromatic anticonvulsants [15,16], in the 1<sup>st</sup> generation we have Phenobarbital, phenytoin, ethosuximide and primidone; the 2<sup>nd</sup> generation to Carbamazepine, oxcarbazepine, benzodiazepines. Our case the patient was under medication with Oxcarbazepine.

The cross-reactivity rate between antiepileptic drugs is greater than 75% [16].

It is important to note that the development of this syndrome is not related to the dose of antiepileptic drug (it is an idiosyncratic reaction) [16].

With regard to treatment as a first measure, the patient must be hospitalized to receive multidisciplinary treatment and establish isolation by contact, to avoid possible infections, in addition to a correct supply of fluids and electrolytes, nutritional management and temperature control. to avoid hypothermia [7].

It is of fundamental importance to suspend the administration of the drug that causes the hypersensitivity reaction, since in this way the risk of mortality of the patient is reduced [2,17].

The use of benzodiazepines is recommended during the acute phase and later (after resolution of the possible hepatic alteration) the use of valproic acid could be assessed [16].

Topical treatment of wounds can be performed with isotonic sodium chloride solutions and subsequently cover the pressure sites with petrolatum until re-epithelialization. It is important to consult with urologists, gynecologists, ophthalmologists and dentists in order to perform the corresponding treatment in each affected area [1,18].

The use of systemic steroids was the standard treatment until 1990, but some authors have reported that no benefit has been proven [19]. Ghislain, in a study of 2002, reported that recovery time did not decrease and they were associated with an increased risk of complications, particularly sepsis and bleeding from the digestive tract [20]. Therefore, it remains very controversial and in a few reports has shown some benefit. Some authors do not recommend its use, as they are associated with increased infections, acid-peptic disease, more days of hospitalization and higher mortality [21]. In contrast other authors have shown that the use of steroids can be effective during the initial erythrodermic phase, using them for a few days and at high doses, 1.5 mg/kg daily dexamethasone intravenously for three days, or 160 to 240 mg daily of methylprednisolone, to decrease the inflammatory process [22,23].

Therefore, the use or not of steroids is still a point of debate.

Other therapeutic measures that have been used are cyclophosphamide and plasmapheresis [24]. Cyclophosphamide has shown favorable results administered at 100 - 300 mg/day [25]. Plasmapheresis has been used in patients who have not shown improvement with supportive treatment and steroid, offering favorable results in a short time [26,27]. Some studies suggest that plasmapheresis should be considered as a first-line adjuvant treatment [28].

There is little evidence of the use of anti-TNF as a treatment in SJS and NET; there are only anecdotal cases reported in the literature [29]. They are considered an emerging and promising therapy based on the selective blockade of TNF- $\alpha$ , which plays a fundamental role in the pathogenesis [30].

### Conclusion

Stevens-Johnson syndrome arises as a systemic disorder that occurs in the skin and mucous membranes related to various factors, such as viral or bacterial infections and, mainly, by the action of specific IgG or IgM antibodies in the administration of medications, in general analgesics and antibiotics.

It is important to make an early diagnosis to suspend the causative agent as soon as possible. There is no consensus that stipulates a single protocol on the treatment of this syndrome, therefore, severity markers must be identified to monitor the evolution and initiate supportive and specific treatment that allows the arrest, cure and prevention of complications and sequels of the disease.

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