

Severe Carbamazepine-Induced Cutaneous Reaction in the Treatment of Post-herpetic Neuralgia. Case Report

João Batista Santos Garcia, TSA ¹, Letácio Santos Garcia Ferro ², Anamada Barros Carvalho ³, Rosyane Moura da Rocha ², Livia Maria Lima de Souza ²

Summary: Garcia JBS, Ferro LSG, Carvalho AB, Rocha RM, Souza LML – Severe Carbamazepine-Induced Cutaneous Reaction in the Treatment of Post-herpetic Neuralgia. Case Report.

Background and objectives: Post-herpetic neuralgia (PHN) is the main complication of herpes zoster. Carbamazepine (CBZ), a well-tolerated anticonvulsant, but frequently associated with severe cutaneous reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is used in the treatment of this complication. The objective of this article was to report a case of SJS/TEN secondary to CBZ in a patient with PHN.

Case report: This is a female patient with continuous severe, burning, chock-like pain in the thoracic region and dorsum associated with reduced strength in the ipsilateral upper limb and diaphoresis. She had crusty and erythematous lesions in the dorsal region of the thorax with allodynia and dysesthesia in the affected dermatome. She was treated with CBZ 300 mg.day⁻¹, amitriptyline (AMT) 12.5 mg at bedtime, and infiltration with local anesthetic in the affected region. After 15 days, she developed malaise, fever, muscle pain, and arthralgia with a mild non-specific cutaneous rash. Carbamazepine was discontinued immediately. One week later, she was hospitalized with urticaria, generalized exanthema, erythematous cutaneous eruptions, bullae, and purpuric maculae all over her body. The impression was of carbamazepine-induced SJS/TEN. She evolved with progressive worsening of her symptoms, with increase in the number and size of cutaneous lesions, besides generalized erythematous macular rash, areas of necrosis, and erosions with symmetrical loosening of the epidermis in face, neck, thorax, dorsum, and limbs, affecting more than 50% of her body surface, besides involvement of buccal, conjunctival, and genital mucosa with vesicular erosions. She had progressive functional worsening, evolving to septic shock and multiple organ failure followed by death.

Conclusions: Stevens-Johnson syndrome and toxic epidermal necrolysis are severe cutaneous reaction with potential for elevated morbidity and mortality that requires immediate intervention and adequate management. In addition, we would like to alert that the use of Carbamazepine should be supervised, especially in the elderly.

Keywords: COMPLICATIONS: toxic epidermal necrolysis, Stevens-Johnson syndrome; DISEASES, Viral: herpes zoster; DRUGS, Anticonvulsant: carbamazepine.

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INTRODUCTION

Post-herpetic neuralgia (PHN) is the main complication of herpes zoster (HZ), resulting from the reactivation of the varicella-zoster virus. Among the drugs used in the treatment of this painful syndrome is carbamazepine (CBZ), a well-tolerated anticonvulsant, but that is frequently associated with severe cutaneous reactions, such as the Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). They

are immunomediated reactions to the drug and can be characterized as a hypersensitivity syndrome due to the preexistence of pharmacogenetic and immunologic abnormalities to the drug. Clinically they present as erythema, necrosis, and extensive sloughing of the epidermis, mucous involvement, and systemic symptoms. Fast diagnosis is essential since withdrawal of the drug is the most important action to minimize the resulting morbidity ^{1,2}. The objective of this article was to report a case of SJS/TEN secondary to CBZ in a patient with PHN.

CASE REPORT

This is a 61 years old female referred in August 2007 to the Outpatient Pain Clinic with a 15-day history of continuous pain in the thoracic region and dorsum irradiating to the left 5th intercostal space, severe (numeric scale at 10), burning, shock-like associated with changes in the strength of the ipsilateral upper limb, and diaphoresis that worsened with cold and improved with butylscopolamine. On physical exam she presented crusty, erythematous lesion in the dorsal region of

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1. Anesthesiology Professor of UFMA; Responsible for the Department of Pain of HU/UFMA and of Instituto Maranhense de Oncologia

2. Physician; Collaborator of the Liga Acadêmica de Dor of UFMA

3. Psychiatrist; Collaborator of the Liga Acadêmica de Dor of UFMA

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correspondence to:
João Batista Santos Garcia
Av. São Marcos, L4, Quadra C, apt 502
65077-310 – São Luís, MA
E-mail: jbgarcia@uol.com.br

the thorax suggestive of herpes zoster infection with severe allodynia and dysesthesia in the affected dermatome. Carbamazepine 300 mg.day⁻¹, and amitriptyline (AMT) 12.5 mg at bedtime were instituted and the affected area was infiltrated with local anesthetic. After 15 days she returned complaining of malaise, fever, muscle pain, and arthralgia with a mild and non-specific rash. It was decided to discontinue the carbamazepine immediately. One week later, she was hospitalized with urticaria and generalized exanthema, erythematous cutaneous eruptions, bullous and macular purpura all over her body. The clinical impression was carbamazepine-induced SJS/TEN (Figure 1). Amitriptyline was maintained and codeine and dypirone were started as adjuvant to pain control. The patient evolved with fast and progressive worsening, with increase in the number and size of the cutaneous lesions. A generalized erythematous rash was observed, as well as areas of necrosis and erosions with symmetrical sloughing of the epidermis in the face, neck, thorax, dorsum, and upper and lower limbs affecting more than 50% of her body surface area; she also had involvement of buccal, conjunctival, and genital mucosa with painful erosions and vesicular lesions. The patient was transferred to the Intensive Care Unit (ICU) with progressive functional worsening of respiratory and cardiovascular systems and after two weeks she developed septic shock and multiple organ failure, following by death.

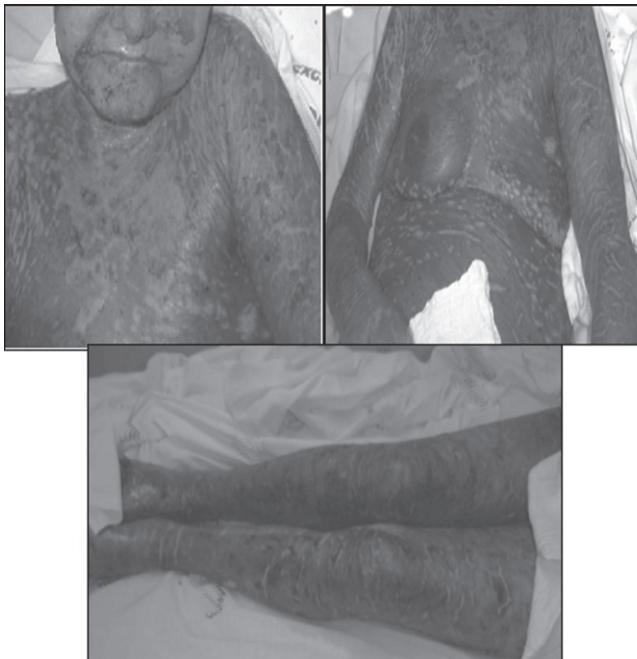


Figure 1 – Face, Thorax, and Upper Limbs Showing Cutaneous Eruptions, Mucous Erosions, and Epidermal Sloughing.

DISCUSSION

The varicella-zoster virus (VZV) remains hidden after penetrating in the nervous system especially in cranial nerves and dorsal root ganglia³⁻⁵. It is frequently reactivated leading to HZ characterized by the presence of erythematous plaques covered with grouped vesicles with unilateral distribution circumscribed to one dermatome, and associated with paresthesia or pain⁶. Among the risk factors, age is the most common being reported mainly in patients over 50-60 years of age^{3,6-8}.

Post-herpetic neuritis, the main complication of HZ, has an incidence that ranges from 10 to 20%, and it is defined as pain that remains after the disappearance of the vesicles of the acute episode after a period of at least 6 weeks^{4,6,9}. Treatment of PHN should be done with drugs to control and relieve the pain. On a recent review^{10,11} the efficacy of existing treatments was classified in categories as first line analgesics in which tricyclic antidepressants, anticonvulsants, and lidocaine patches (proven efficacy) were included; and second line analgesics, in which opioids were included. Neural blocks could also be considered potential treatment^{11,12}. Although less effective and with more side effects^{11,13,14} carbamazepine still is an anticonvulsant commonly used in the treatment of PHN^{9,15,16}.

Cutaneous reactions to drugs are common, affecting 2% to 3% of hospitalized patients. Fortunately the majority of the reactions are not severe, and very few are fatal. Some clinical and laboratorial signs can be found in the suspected diagnosis of severe cutaneous reactions, and can be considered an alert for our initial recognition (Chart 1)¹⁷.

When our patient returned to the clinic after 15 days she presented fever, malaise, and non-specific cutaneous rash. Despite discontinuing CBZ, one week later her state was more severe. We were facing a diagnostic challenge since our hypothesis of

Chart 1 – Clinical and Laboratorial Picture that Alert for Drug-Induced Reactions

Clinical Picture	Clinical picture
Cutaneous	Eosinophilia (> 1000 cel/mm ³)
Confluent erythema	Lymphocytosis with atypical lymphocytes
Pain	
Epidermal necrosis	
Facial edema	
Palpable purpura	
Pustules or epidermal sloughing	
Positive Nikolsky sign	
Mucosal erosions	
Urticaria	
Tongue edema	
General	
High fever (> 40°C)	
Adenomegaly	
Arthralgia or arthritis	
Hypotension	

Source: Adapted from Roujeau and Stern (1994).

SJS/TEN represented an intense idiosyncratic reaction, not too frequent, but caused by drugs and with a significant mortality rate^{18,19}. Initially, it was considered that SJS was similar to major erythema multiforme (EM) until less than two decades ago some authors proposed that they are two distinct disorders with similar mucous erosions, but with clinical differences and in the pattern of the cutaneous lesions^{7,20-24} (Chart 2).

It was proposed in additional studies that SJS and TEN are the same disease, but with distinct severity. A recent classification proposed that sloughing of the epidermis or positive Nikolsky sign in SJS is limited to 10% of the body surface area (BSA); in the transition of SJS/TEN it is limited to between 10 and 30% of BSA; and in TEN the sloughing of the necrotic epidermis is greater than 30% of BSA^{18,21-23,25-28}.

Several estimates of the incidence of SJS, superposition of SJS/TEN, and TEN are referred due to the spectrum and clinical variability. However, as a rule the estimate ranges from 1 to 6 and 0.4 to 1.3 cases per million individuals a year for SJS and TEN respectively^{19,21}. Both adults and children are involved, but it is more common in females. The age of patients with SJS ranges from 25 to 47 years while TEN affects older patients from 46 to 63 years¹⁸.

Chart 2 – Characteristics and Comparison between Erythema Multiforme and Stevens-Johnson Syndrome/Toxic epidermal Necrolysis

Erythema Multiforme	Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis
Infection: herpes simplex virus, Mycoplasma	Drug-induced
Lesions: erythematous papules	Lesions: dark macula
Involvement of three regions	Atypical involvement
Without fever and other constitutional symptoms	Fever, headache, myalgia
Up to 10% of the body surface area	Extensive epidermal necrolysis
Moderate course, recovery in 1-4 weeks	Elevated mortality in severe cases
Recurrence is common, related to herpes simplex	Recurrence is uncommon, related to the presence of the drug

Source: Adapted from Fritsch and Maldonado (2003).

Chart 3 – Drugs and Risk of the Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

High Risk	Low Risk
NSAIDs (Oxicam)	Aminopenicillins
Allopurinol	Cephalosporins
Carbamazepine	Fluoroquinolones
Phenytoin	Macrolides
Phenobarbital	
Lamotrigine	
Sulfadiazine	
Sulfamethoxazole	
Sulfapyridine	

Source: Adapted from Fritsch and Maldonado (2003).

Although the etiology of SJS/TEN is multiple it is commonly triggered by viral infections (herpes simplex virus is the infectious agent more commonly involved)²⁹ and neoplasias (carcinomas and lymphomas). However, the most common cause is the use of drugs ranging from 80% to 95% for TEN, and 30% to 50% for SJS. Among the drugs implicated more often are allopurinol, antibiotics (sulfonamides, penicillins, cephalosporins), anticonvulsants (carbamazepine, lamotrigine, phenobarbital), and non-steroid anti-inflammatories (NSAIDs)^{17-19,21,23,30,31}.

In the decade of 1990 a quantitative case-controlled study on the relative risk of SJS/TEN with those drugs which confirmed a substantial increase in their risk was published³². In 2007, a multinational study involving Europe and Israel (EuroSCAR) concluded that allopurinol was the most common cause of SJS/TEN in those areas^{18,27,33}. More recently, in a seven-year study Devi K et al. concluded that anticonvulsants were the cause implicated more often in SJS/TEN especially in the first eight weeks of treatment³⁴, and the main drug responsible (more than 80%) was carbamazepine³⁵ (12-20 days)³⁶. In a retrospective study conducted in 2008 SJS/TEN was more common with the use of anticonvulsants, antibiotics, and ANSAIDs³⁷. Prescribing those drugs requires deep assessment of the expected benefits³⁶, with recommendation of gradual titration at the beginning of treatment especially with anticonvulsants^{18,38} (Chart 3).

Typically, the initial presentation is marked by a prodrome of fever, and symptoms resembling infection with influenza for 1 to 3 days before the development of cutaneous lesions. Pain and burning of the eyes develop progressively, announcing the involvement of mucous membranes and rapid progression of systemic signs and symptoms^{18,19,27}. The skin lesions are symmetrical and begin with a confluent erythema, papules, vesicles, bullae, or urticarial plaques with the center of the lesions with a vesicular, purpuric, or necrotic aspect affecting face, upper part of the trunk, and proximal extremities that progresses rapidly to involve the remaining areas. The pathognomonic lesion has the appearance of a bull's eye, and it can evolve, coalesce, or increase in size and number. Thus, Nikolsky sign (sloughing of the skin with mild friction) can be present and make it susceptible to secondary infection. Mucous involvement is seen in 90% of the cases, preceding or succeeding the cutaneous involvement^{17-19,27}.

The evolution gives rise to erosions in the mucous membranes with formation of pseudomembranous formations on the eyes, mouth, genitals, and oropharynx. Exposure to the drug precedes the onset of symptoms by one to three weeks^{17,21,27}. The time of evolution of SJS/TEN from the beginning of the prodrome until the hospitalization in the absence of significant complications ranges from one to four weeks¹⁸. Finally, visceral involvement including pulmonary, renal, and gastrointestinal tract is also possible. The severity is proportional to the extension of skin necrosis, which gives patients the aspect of large burns leading to loss of proteins and electrolytes, bacterial colonization, infection, and sepsis^{17,26,39}.

Diagnosis is clinical; however, skin biopsy for histological routine and immunofluorescence study should be done in all

cases of epidermal necrolysis to exclude differential diagnosis and of definitive confirmation^{17-19,27}. Regarding the laboratorial diagnosis the CBC can reveal important anemia and lymphopenia, eosinophilia, and neutropenia, and the latter is related to a worse prognosis. Moderate elevation of hepatic enzymes and amylase are frequent as well as altered renal function^{17,19,21}. Blood, urine, and wound cultures are indicated when subjacent infection is suspected. In TEN cutaneous biopsy shows the dermis with a minimal infiltrate of inflammatory cells predominating T lymphocytes CD4+, necrosis of the epidermis in which predominated T lymphocytes CD8+, and abundant deposits of tumor necrosis factor-alpha (TNF- α).

In patients with SJS the dermal-epidermal junction has vacuolar alterations and subepidermal blisters. The dermal infiltrate is superficial and for the most part perivascular, and on electron microscopy the conjunctiva reveals squamous epithelial metaplasia, vascular disruption, and reduplication²¹. In the present case, the hypothesis of SJS/TEN was made by the percentage of epidermal sloughing, but a biopsy to confirm the diagnosis was not possible.

In 2007, on an information released by the FDA (Food and Drug Administration) drug-induced fatal cutaneous reactions (SJS/TEN) are more common in patients with a particular allele of the human leukocyte antigen (HLA), HLA-B*1502. This

allele is seen almost exclusively in patients from some areas of Asia. Genetic testing in patients with ancestors from areas in which HLA-B*1502 should be evaluated for this allele before the onset of treatment with carbamazepine. If the test is positive, this drug should not be initiated unless the expectation of benefits is clearly superior to the increased risk of cutaneous reactions. This is true for patients of any ethnicity and genotype including patients positive for HLA-B*1502⁴⁰⁻⁴³.

The main therapeutic action in SJS/TEN is the early recognition of the reaction and withdrawal of the drug, since the delay can be seriously deleterious for the patient. The management of the patient involves specific care and in most cases transference to the intensive care unit^{28,39,44}.

Mortality in SJS/TEN is approximately 5%, but it is increased with an increase in the age of the patient and in the area of epidermal sloughing. As a rule, skin lesions do not leave scars, but mucous lesions could be a late complication, and they can cause bleeding and narrowing of affected areas⁴⁵.

Stevens-Johnson syndrome and TEN represent a serious cutaneous reaction with the potential for elevated morbidity and mortality, which require fast and adequate management. One should always remember that the use of carbamazepine should always be under supervision, especially in the elderly.

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Resumen: Garcia JBS, Ferro LSG, Carvalho AB, Rocha RM, Souza LML – Reacción Cutánea Grave Inducida por la Carbamazepina en el Tratamiento de la Neuralgia Postherpética. Relato de Caso.

Justificativa y objetivos: El herpes zoster tiene como principal complicación la neuralgia postherpética (NPH). Para su tratamiento se usa la carbamazepina (CBZ), un anticonvulsivo bien tolerado, pero que sin embargo está a menudo asociado a reacciones cutáneas graves, como por ejemplo, el síndrome de Stevens-Johnson (SSJ) y la necrólisis epidérmica tóxica (NET). El objetivo de este trabajo es relatar un caso de SSJ/NET secundario al uso de CBZ en paciente con NPH.

Relato del caso: Paciente del sexo femenino, con dolor continuo e intenso en la región torácica y dorso, ardor, punzada, descarga eléctrica, alteración de fuerza del miembro superior ipsilateral y sudoración. Presentaba lesiones de postillas y eritemas en la región dorsal del tórax, con alodinia y disestesias en el dermatoma acometido. Se inició CBZ 300 mg.día⁻¹, amitriptilina (AMT) 12,5 mg por la noche e infiltración con anestésico local en la región afectada. Después de 15 días, el paciente decía sentir un fuerte malestar, fiebre, dolores musculares y artralgias con rash cutáneo ligero e inespecífico. Se le retiró la carbamazepina inmediatamente. Una semana después fue ingresado con urticaria y exantema generalizados, erupciones cutáneas eritematosas, burbujas y marcas purpúricas por todo el cuerpo. La impresión era de SSJ/NET inducida por carbamazepina. Hubo un progresivo empeoramiento del cuadro, con aumento del número y del tamaño de las lesiones cutáneas, además de rash eritematoso macular generalizado, áreas de necrosis y erosiones simétricas de la epidermis en la cara, cuello, tórax, dorso y miembros, llegando a más del 50% del área de superficie, además de la involucración de la mucosa bucal, conjuntival y genital con erosiones vesiculares. Presentó un empeoramiento funcional progresivo, evolucionando con choque séptico y fracaso multiorgánico, lo que produjo finalmente su deceso.

Conclusiones: La SSJ/NET es una reacción cutánea grave con potencial para la morbilidad y mortalidad elevadas y que exige una intervención rápida y un manejo adecuado. También alertamos sobre el uso de la carbamazepina, que debe siempre ser inspeccionado, especialmente en los ancianos.