



## Toxic epidermal necrolysis induced sulfametoxazol-trimetoprina associated with brain injury

Juliana Mara Silva<sup>1</sup>, Vanessa de Paula Tiago<sup>2</sup>, Cristhiane Borges Juliano<sup>2</sup>, Valéria Cardoso Alves Cunali<sup>3</sup>, Renata Cristina Franzon Bonatti<sup>4</sup>

### Keywords:

ataxia,  
brain Stem,  
mucous membrane,  
psychomotor agitation,  
trimethoprim,  
ulfamethoxazole  
drug combination.

### Abstract

Toxic epidermal necrolysis also known as Lyell syndrome, is a rare and severe adverse reaction predominantly affecting the skin and mucous membranes. It is characterized by the widespread death of keratinocytes of the epidermis and dermal-epidermal junction levels. The skin manifestations include maculopapular rash, similar to a morbilliform rash that precedes the formation of sero-hematic content blisters, mucosal erosions and subsequent detachment of the epidermis, reaching over 30% of the total body surface. It has a low incidence and high mortality, setting an extremely serious situation and therefore should be readily recognized. This article reports the case of a patient with clinical and pathology consistent with toxic epidermal necrolysis triggered by the use of antibiotic sulfamethoxazole- trimethoprim, with the addition of characteristic mucocutaneous involvement and associated neurological complications such as ataxia, disorientation, seizures, aphasia and dystonia.

<sup>1</sup> Resident in Pediatrics, Uberaba, MG, Brazil.

<sup>2</sup> Resident in the Pediatric Intensive Care Unit, Uberaba, MG, Brazil.

<sup>3</sup> Associate Professor of Pediatrics - Professor of Pediatrics, Uberaba, MG, Brazil.

<sup>4</sup> Associate Professor of Neuropediatrics - Professor of Neuropediatrics, Uberaba, MG, Brazil.

### Correspondence to:

Juliana Mara Silva.

Clinical Hospital of Triângulo Mineiro Federal University. Rua Constituição, nº 1180, Apto 203, Bairro Abadia Uberaba - MG, Brazil. CEP: 30110-025. E-mail: jms\_med@hotmail.com

## INTRODUCTION

Adverse reactions to drugs are relevant complications of drug therapy<sup>1</sup>. Toxic epidermal necrolysis (TEN) is a serious and rare disease with an estimated incidence of 0.4-1.2 cases/million people per year<sup>2</sup>. Women are more frequently affected, with approximately three women with TEN for every two men<sup>3</sup>.

It may be triggered by infections, but it is believed that at least 80% of cases are caused by medications<sup>2,4</sup>. The pharmaceuticals worth mentioning are sulfonamides, allopurinol, carbamazepine, phenytoin, and phenobarbital<sup>2,3</sup>.

It is a disease with multisystem impacts, and its clinical presentation includes skin and mucosal changes that affect more than 30% of the total body surface<sup>5,6</sup>.

There were no reports found in the literature directly associating TEN with neurological signs and symptoms similar those presented by the patient herein.

## CASE REPORT

Eight-year-old girl with a history of upper respiratory infection and taking trimethoprim-sulfamethoxazole presented with diffuse pruritic rash, mucopurulent exudate in the oropharynx and the tonsillar pillars. She developed a worsening of the rash, neurological deterioration with confusion, reduced level of consciousness, disorientation, ataxic gait, choreiform movements in the upper limbs, and mild edema in the face and neck.

Presence of exudative plaque in the oropharynx and tonsils. She developed hemodynamic instability, generalized tonic-clonic seizures, laryngeal stridor, anasarca (which was worse in the face, torso, and limbs), worsening level of consciousness (Glasgow coma scale score of 6), hypertonia on the right side of her body, dystonic posturing, asymmetrical mydriatic, and poorly reactive pupils, generalized hyperreflexia, bilateral Babinski sign. Accentuation of the maculopapular rash with violet discoloration of the skin and bullous lesions with a positive Nikolsky sign (Figure 1).

From a dermatological standpoint, the maculopapular rash lesions developed diffusely and progressed to confluent lesions with a change from violet to purple coloring and flaccid bullae associated with ulcers, including in the oral and vaginal mucosa (Figure 2).

An incisional skin biopsy was performed, the histopathological analysis of which revealed the presence of subepidermal blisters, necrotic keratinocytes in the epidermis, exocytosis of lymphocytes and mononuclear infiltrate with bleeding. These findings were compatible with TEN.

The neurological symptoms improved, and there were signs of a behavioral disorder characterized by mood swings (euphoria/depression).



Figure 1. Maculopapular lesions with purple coloring.



Figure 2. Lesion involving the vaginal mucosa.

## DISCUSSION

TEN is characterized by extensive detachment of the epidermis secondary to necrosis. The pathogenesis is still not well understood, but it is based on a delayed hypersensitivity reaction to drugs in individuals with greater genetic predisposition<sup>5-7</sup>.

After contact with the causative agent, prodromal symptoms (fever, rhinitis, cough, chest pain, myalgia, anorexia, and asthenia) begin. They precede the onset of mucocutaneous lesions characteristic of the acute phase, which lasts 2-12 days<sup>1,3,4</sup>. Cutaneous involvement is marked by an itchy, painful rash that primarily affects the face and upper torso, with craniocaudal progression<sup>1,3</sup>.

Erythema may be macular with irregular contours and a darker center, reaching its largest size after three days<sup>1,3,7</sup>. The culmination of the process is the characteristic denudation of the necrotic epidermis, which is marked by the detachment of sheets<sup>1</sup>. The epidermis exhibits serous, flaccid, and confluent blisters that burst and open, giving the patient the appearance of having a large burn<sup>1,7</sup>.

The Nikolsky sign is positive, and mucosal lesions appear before epidermal necrosis with erosion and peeling of conjunctival, oro-pharyngeal, nasal, esophageal, urethral, anal, vaginal, and perineal mucosa<sup>1</sup>.

It is a self-limiting disease, but complications are serious and potentially life-threatening. Secondary infection is the most severe complication, and sepsis is responsible for over 50% of the cases of death<sup>4,5</sup>. The loss of the skin barrier enables bacterial invasion of exogenous or endogenous origin<sup>3</sup>. Psychomotor agitation and confusion are not uncommon and are usually indicative of hemodynamic complications and sepsis<sup>1</sup>.

Ocular involvement may be present in 39% to 61% of cases and includes complications such as corneal ulcers, anterior uveitis, and panophthalmitis<sup>5</sup>.

Respiratory changes are common, and 10 to 20% of patients may require artificial ventilation<sup>3</sup>. Gastrointestinal adhesions are not uncommon, nor are urinary incontinence, vaginal stenosis, renal tubular necrosis, renal failure, skin ulcers with re-infection, and non-esthetic scars<sup>5</sup>.

In 90% of cases, blood disorders such as anemia and leukopenia with lymphopenia are due to a temporary depletion of CD4 + T lymphocytes, and in 30% of cases, neutropenia is usually associated with the onset of sepsis and poor prognosis. Thrombocytopenia is more uncommon, and occurs in 15% of patients<sup>3</sup>.

Neurological abnormalities found in the acute phase of the disease are not described in the literature. Clinically, this patient exhibited signs of impairment of the posterior fossa, brainstem, basal ganglia, and cerebral cortex (seizures), all of which suggested posterior reversible encephalopathy syndrome (PRES) as a differential diagnosis.

It is characterized by headaches, visual disturbances, a decreased level of consciousness, and seizures, and it is associated with probable vasogenic edema in the white matter of the brain, which predominantly affects the occipital and parietal lobes<sup>8</sup>. Several factors can trigger this syndrome, the most common of which are acute high blood pressure, impaired renal function, and immunosuppressive therapy. Other possible etiologies are eclampsia, systemic lupus erythematosus, transplantation, cancer and cancer treatment, systemic infections, and acute or chronic kidney disease<sup>9</sup>.

The diagnosis of TEN requires compatible clinical presentations and support from a recent history of drug administration<sup>6,7</sup>. The diagnosis is confirmed by histopathological analysis that demonstrates the existence of vacuolization of the basal membrane, formation of subepidermal blistering, and necrosis of epidermal keratinocytes<sup>4,7</sup>. The identification of the drug that caused the reaction and its early withdrawal are the most important therapeutic measures, and the delay of this process may be deleterious to the patient<sup>5-7</sup>.

Supportive treatment is similar to that provided to patients with extensive burns<sup>2-4</sup>. Antibiotic therapy should be initiated only when there is suspicion of bacterial infection<sup>6</sup>.

Although the literature includes cases successfully treated with oral corticosteroids, immunosuppressants, anti-TNF agents, plasmapheresis and IV immunoglobulin therapy, there is still no consensus regarding treatment for this condition<sup>6</sup>.

## CONCLUSION

We present a severe case of TEM accompanied by lesions in the brain stem with a good outcome despite the potential risk. Although TEM is not associated with brain stem injury in the literature, this complication, which can be triggered by inflammatory/infectious processes, should be considered.

## REFERENCES

1. Criado PR, Criado RFJ, Vasconcellos C, Ramos RO, Gonçalves AC. Reações cutâneas graves adversas a drogas - aspectos relevantes ao diagnóstico e ao tratamento - Parte I - Anafilaxia e reações anafilactóides, eritrodermias e o espectro clínico da síndrome de Stevens-Johnson & necrólise epidérmica tóxica (Doença de Lyell). *An Bras Dermatol*. 2004;79(4):471-88. DOI: <http://dx.doi.org/10.1590/S0365-05962004000400009>
2. Oliveira FL, Silveira LK, Morais TS, Serra MCVF. Necrólise epidérmica tóxica e síndrome de Stevens Johnson: atualização. *Rev Bras Queimaduras*. 2012;11(1):26-30.
3. Cabral L, Diogo C, Riobom F, Teles L, Cruzeiro C. Necrólise epidérmica tóxica (Síndrome de Lyell): uma patologia para as Unidades de Queimados. *Acta Med Port*. 2004;17(2):129-40.
4. Meira Júnior JD, Souza JT, Toniollo CF, Stolf HO. Necrólise epidérmica tóxica/síndrome de Stevens-Johnson: emergência em dermatologia pediátrica. *Diagn Tratamento*. 2015;20(1):8-13.

5. Bulisani ACP, Sanches GDS, Guimarães HP, Lopes RD, Vendrame LS, Lopes AC. Síndrome de Stevens-Johnson e necrólise epidérmica tóxica em medicina intensiva. *Rev Bras Ter Intensiva*. 2006;18(3):292-7. DOI: <http://dx.doi.org/10.1590/S0103-507X2006000300012>
6. Wong A, Malvesti AA, Hafner MFS. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review. *Rev. Assoc. Med. Bras*. 2016; 62 : 1e. <http://dx.doi.org/10.1590/1806-9282.63.02.148>
7. Oliveira A, Sanches M, Selores M. O Espectro Clínico Síndrome de Stevens-Johnson e Necrólise Epidérmica Tóxica. *Acta Med Port*. 2011;24(S4):995-1002.
8. Fernandes FJF, Machado Júnior MAC, Pedreira AV, Silva CIS, Tavares HC, Barbosa VA. Síndrome de Encefalopatia Posterior Reversível. *Arq Neuropsiquiatr*. 2002;60(3-A):651-5.
9. Marrone LCP. Síndrome da encefalopatia reversível posterior: aspectos clínicos, imunológicos e experimentais [Dissertação de mestrado]. Porto Alegre: Pontifícia Universidade Católica do Rio Grande do Sul, Faculdade de Medicina; 2012.