Cotrimoxazole Induced Toxic Epidermal Necrolysis: A Clinical Case

Necrólise Epidérmica Tóxica Induzida por Cotrimoxazol: Um Caso Clínico

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Abstract:

We present the case of a 53-year-old man, with no relevant personal medical history who was on the seventeenth day of treatment with cotrimoxazole after a diagnosis of a urinary tract infection.

He was admitted to the emergency department complaining of a pruritic maculopapular rash that was widespread, with particular emphasis on the torso and sparing the palms of the hands and soles of the feet, bilateral conjunctival hyperemia, lip edema, and odynophagia.

After an extensive study was conducted, the conclusion was that it was a side effect of the ongoing treatment, and the antibiotic was promptly suspended. However, the skin and mucosal lesions progressed unfavorably, with an increase in the affected area and an important involvement of the oral and ocular mucosa with extensive erosions. The diagnosis of toxic epidermal necrosis was made, a rare entity that occurs as a side effect of commonly prescribed antibiotics and other drugs.

Keywords: Stevens-Johnson Syndrome/etiology; Trimethoprim, Sulfamethoxazole Drug Combination/adverse effects.

Resumo:

Os autores apresentam o caso de um doente do sexo masculino com 53 anos de idade, sem antecedentes patológicos de relevo, que se encontrava no 17º dia de tratamento com cotrimoxazol após um diagnóstico de prostatite.

O doente recorreu ao serviço de urgência por apresentar um *rash* maculopapular pruriginoso generalizado, mais acentuado no tronco e que poupava as palmas e plantas, hiperemia conjuntival bilateral, edema dos lábios e odinofagia.

Após investigação, concluiu-se que o quadro clínico seria mais provavelmente resultado do tratamento em curso, pelo que se suspendeu prontamente o antibiótico. No entanto, as lesões mucocutâneas agravaram, com um aumento da área afectada e um importante envolvimento da mucosa oral e ocular, com erosões extensas. Foi então feito o diagnóstico de necrólise epidérmica tóxica, uma entidade rara que pode surgir como efeito lateral da toma de alguns fármacos comumente prescritos na prática clínica diária.

Palavras-chave: Combinação Trimetoprima e Sulfametoxazol/efeitos adversos; Síndrome Stevens-Johnson/etiologia.

Learning Points

1. Antibiotics are one of the most prescribed drugs in the emergency department and their side effects are usually manageable, but in rare cases, they can lead to fatal outcomes.
2. Toxic epidermal necrolysis is a rare and potentially fatal mucocutaneous illness and up to a third of cases is associated with commonly prescribed antibiotics.
3. Clinical suspicion is of critical significance in these cases, since early diagnosis and support treatment can greatly improve prognosis and outcome.

Introduction

Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and potentially fatal mucocutaneous illnesses. The majority of cases are related to drugs, mostly antibiotics.[1]

These entities are characterized by extensive necrosis and detachment of the epidermis. There is mucocutaneous involvement in most patients, namely ocular, oral, and genital. Most authors argue that these two entities represent a continuum of the same pathology and are mainly distinguished by their severity, based on the percentage of body surface area affected by blisters and erosions. SJS presents with less than 10% of surface body area affected, and TEN affects 30% or more of surface body area. In either case, the symptoms start 7 to 21 days after the start of therapy with the responsible drug. In the present case, the authors describe a case of cotrimoxazole induced TEN.

Case Report

We describe the case of a 53-year-old male without significant previous medical history who, at the time of admission, was on the seventeenth day of treatment with cotrimoxazole for a diagnosis of urinary tract infection.

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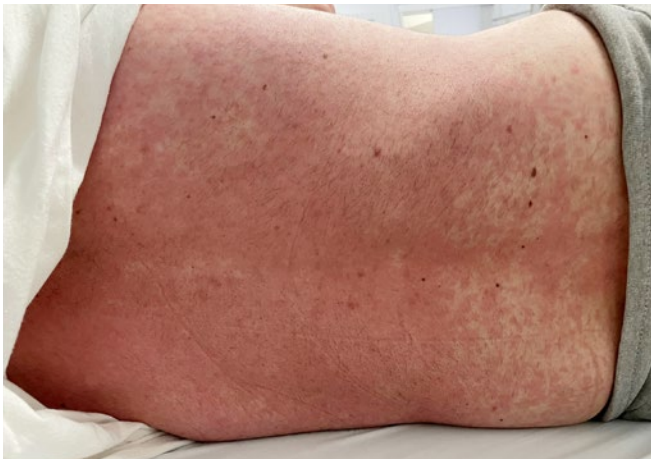

Figure 1: Picture of the patients torso showing a maculopapular rash.

The patient was admitted to the emergency department complaining of a widespread pruritic maculopapular rash (Fig. 1) with particular emphasis on the torso; sparing the palms of the hands and soles of the feet; bilateral conjunctival hyperemia with hemorrhagic suffusion on the right eye (Fig. 2), lip edema and odynophagia. Upon admission, the patient reported experiencing two days of generalized malaise, headaches, and myalgias.

An extensive study was conducted and after excluding other causes, we came to the conclusion that it most likely was a side effect of the ongoing antibiotic treatment.

A thoraco-abdomino-pelvic computed tomography was performed, no hepatic involvement was found; no significant alterations were discovered in the other segments visualized.

Hematologically, the patient presented with leukopenia and thrombocytopenia; the eosinophilic count was normal.

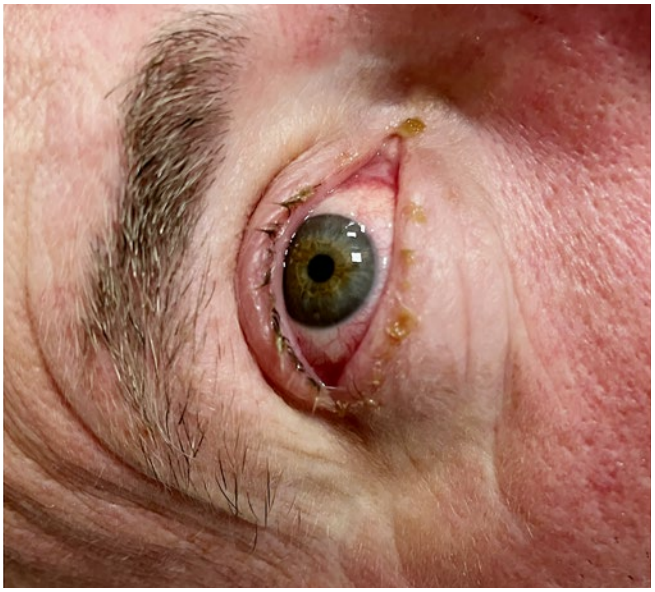

Figure 2: Hemorrhagic suffusion of the patients right eye and purulent secretions.

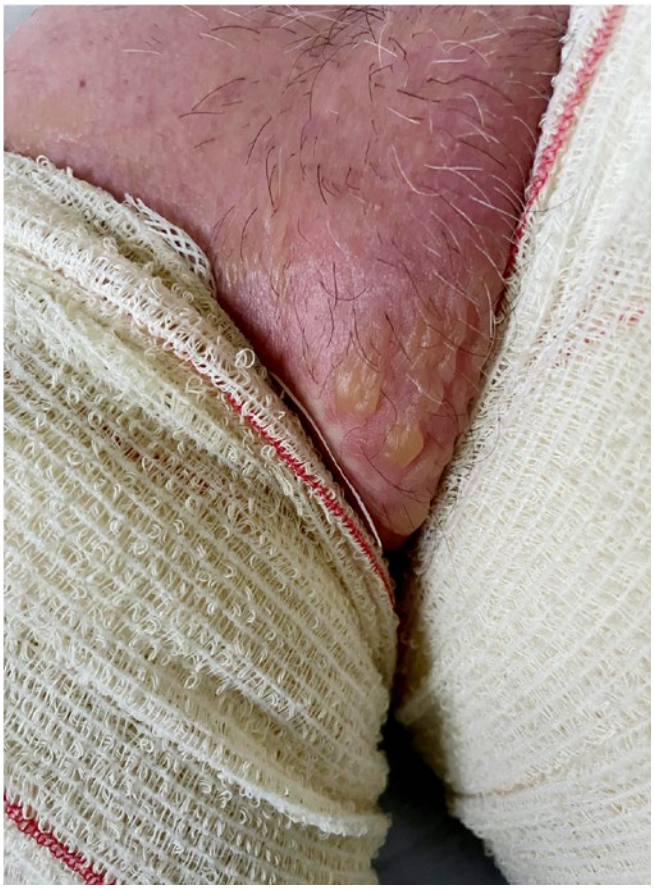

Figure 3: Patients skin with extensive bullae, protected with bandages.

The antibiotic was promptly suspended, but despite this, the overall state of the patient declined.

The skin and mucosal lesions worsened significantly, with an increase in the affected area, the development of extensive bullae (Fig. 3), a positive Nikolsky sign and an important involvement of the oral mucosa with extensive erosions that made eating and hydrating very difficult (Fig. 4).

Ocular involvement also worsened, resulting in the emergence of erosions on the cornea of the right eye.

Since the affected body area was superior to 30%, a diagnosis of TEN was assumed.

The patient was transferred to the Burn Center, for treatment and stabilization. There, he underwent support treatment (volemic resuscitation, nutritional support and wound dressing) and immunosuppressive treatment with cyclosporine (200 mg/day) and topical steroids for the ocular lesions.

The patient was discharged, with no sequelae to the skin, but the ocular erosions continue being treated.

During the time the patient was hospitalized and during follow-up consultations, an extensive complementary study was performed - no sexually transmitted infections (STI) were found, viral serologies were negative and no evidence of a malignant disease was found, all of which are known risk factors for the disease.

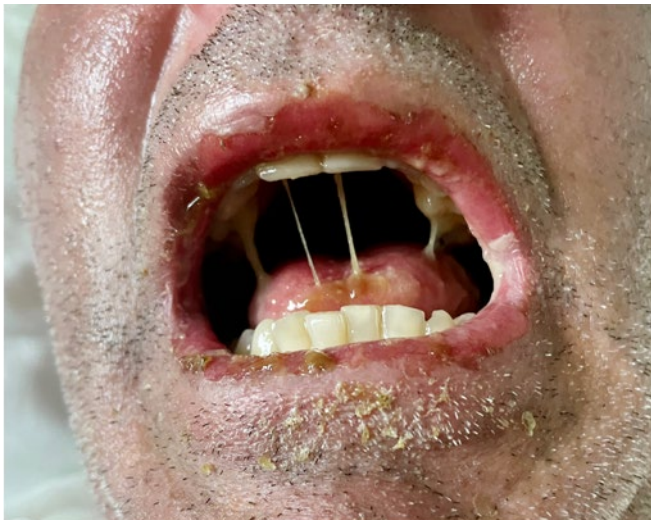

Figure 4: Significant erosions of the oral mucosa.

Discussion

SJS and TEN are reported to affect 1 to 10 individuals per million population per year; it has been reported in all age groups and the most common trigger identified is drugs[1] (Table 1).

Among all drugs described as a cause for these pathologies, antibiotics are reported to account for almost a third of the cases, and sulfonamide antibiotics as the leading class to cause these reactions.[2]

In the case we present the mucosal involvement is clear: there were ocular and oral erosions and lesions, severe enough to cause difficulty eating and drinking.

The diagnosis of SJS and TEN is mostly clinical: a detailed clinical history reporting the use of a potentially associated drug, compatible mucocutaneous erosions and lesions, and a flu-like prodromal syndrome of malaise, fever and cough.

Following this, a skin eruption occurs: it usually begins in the trunk area and becomes generalized. The palms and soles are typically spared. Erythematous macules appear, with areas of confluence, primarily in the trunk region. Within a short period, there is progression of the condition, with detachment of the epidermis, forming blisters that easily detach with minimal trauma, creating areas of erosion of varying size. The Nikolsky sign appears in the perilesional areas and is characterized by epidermal detachment with tangential digital pressure.

The course of disease seen with our patient coincides with the most common form of presentation of this disease, clinically and chronologically: the symptoms started 7 to 21 days after initiating a potentially culprit drug, with a flu-like prodromal syndrome, followed by a skin eruption in the trunk that generalized.

The differential diagnosis includes other desquamating and vesiculobullous dermatoses, including pemphigus vulgaris, staphylococcal scalded skin syndrome and erythema multiforme major (EMM). EMM and SJS/TEN were once classified as a spectrum of the same disease, but later distinguished as different diseases.[4]

Table 1: Drugs related with SJS and TEN.

Antibiotics	Sulfonamides, Beta-lactams, macrolids, fluoroquinolones, anti malarial drugs
Anticonvulsants	Carbamazepine, lamotrigine, phenobarbital, phenytoin
Non-steroidal anti-inflammatories (NSAIDs)	Piroxicam
Other	Allopurinol, nevirapine

The pathophysiological mechanisms that lead to these conditions are incompletely understood. CD8+ cytotoxic T cells and natural killer (NL) cells are thought to play an important role, producing several cytokines and cytotoxic proteins (including soluble Fas ligand, tumor necrosis factor (TNF)-alpha and most recently, a cytolytic protein – granulysin) that play a key role in the pathogenesis of the disease.

A mortality rate of 30%-50% has been reported as a result of these conditions, mostly as a result of sepsis, a complication to which these patients are highly susceptible.[2,3]

There is also a high morbidity rate, namely due to mucosal erosions and lesions. Most patients present with involvement of two or more mucosal surfaces; oral mucosa is the most frequently affected and ocular lesions are also frequent (as seen in the case described here).[4] Gastrointestinal and gynecologic involvement have also been reported.[3]

In Table 2 we outline some of the distinguishing characteristics of SJS/TEN and EMM.

The most important component of the management of this illness remains the early diagnosis, the precocious withdrawal of the responsible drug, supportive treatment and specialist wound care.[3]

There are several reports of multiple adjunctive therapies (including corticosteroids, intravenous immunoglobulins, cyclosporine and TNF antagonists), but there is still no consensus on the most effective one.[4] This may happen because due to the rarity of this entity, few prospective studies have tested the true efficacy of specific therapies.

Table 2: Distinguishing characteristics of SJS/TEN and EMM.

Parameters	SJS/ TEN	EMM
Characteristic lesions	Atypical target lesions: macules with central clearing; Large sheets of painful desquamation in later lesions;	Typical target lesions: papules with a dark center and 3 well-demarcated, concentric components;
Distribution	Beginning on the face and trunk – spreading is centrifugal;	Face and acral skin, rare involvement of trunk;
Triggers	Mostly drugs (Table 1);	Infection (*M. pneumonia* and herpes simplex virus);
Mucosal Involvement	Majority of the cases;	Rare;
Recurrence	Rarely seen once the causative drug is removed and avoided;	Frequent;

In the specific case of our patient, along with supportive treatment and specialist wound care in a Burn Center, the medical team agreed to administer cyclosporine, obtaining a positive response with improvement of skin lesions.

Early clinical awareness is, therefore, of primordial importance. Supportive treatment, suspension of the culprit drug and specialized wound treatment are the only interventions proven to change the outcome for the patients.

The purpose of this case is to demonstrate the value of early recognition of the signs and symptoms of the disease in order to prevent a delay in diagnosis and an increase in morbidity and mortality rates. ■

Contributorship Statement

CV - Data collection and interpretation, manuscript writing.
GP - Data collection, critical revision of the manuscript.
RS - Data interpretation and analysis, literature review.
IC - Literature review, data interpretation, critical revision of the manuscript
CC - Data collection, analysis and interpretation, critical revision of the manuscript.
All authors approved the final version to be published.

Declaração de Contribuição

CV – Aquisição e interpretação de dados, redação do artigo.
GP – Aquisição de dados, revisão crítica do artigo.
RS – Interpretação e análise de dados, revisão da literatura.
IC – Revisão da literatura, interpretação de dados, revisão crítica do artigo.
CC – Aquisição, análise e interpretação de dados, revisão crítica do artigo.
Todos os autores aprovaram a versão final a ser publicada.

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