Stevens-Johnson syndrome and toxic epidermal necrolysis: a review

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Summary

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are uncommon, acute and potentially life-threatening adverse cutaneous drug reactions. These pathologies are considered a hypersensitivity reaction and can be triggered by drugs, infections and malignancies. The drugs most often involved are allopurinol, some antibiotics, including sulfonamides, anticonvulsants such as carbamazepine, and some non-steroid anti-inflammatory drugs (NSAIDs). Necrosis of keratinocytes is manifested clinically by epidermal detachment, leading to scalded skin appearance. The rash begins on the trunk with subsequent generalization, usually sparing the palmoplantar areas. Macular lesions become purplish, and epidermal detachment occurs, resulting in flaccid blisters that converge and break, resulting in extensive sloughing of necrotic skin. Nikolsky's sign is positive in perilesional skin. SJS and TEN are considered to be two ends of the spectrum of one disease, differing only by their extent of skin detachment. Management of patients with SJS or TEN requires three measures: removal of the offending drug, particularly drugs known to be high-risk; supportive measures and active interventions. Early diagnosis of the disease, recognition of the causal agent and the immediate withdrawal of the drug are the most important actions, as the course of the disease is often rapid and fatal.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, drug eruptions.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are uncommon, acute and potentially life-threatening adverse cutaneous drug reactions, often related to drug use. They are the result of extensive death of keratinocytes, which leads to the separation of areas of skin in the dermal-epidermal junction, producing the appearance of scalded skin. The disease runs an unpredictable course: An initially benign-appearing dermatosis can progress rapidly.[1-5]

Stevens and Johnson described in 1922 two cases of patients with generalized skin rash, continuous fever, stomatitis and severe purulent conjunctivitis. In 1950, this clinical picture was divided into two categories: erythema multiforme minor (Von Hebra) and erythema multiforme major (EMM).[2,4] As of 1983, the eponymous term Stevens-Johnson began to be used interchangeably with EMM.[2,4]

Only in 1993, Bastuji-Garin et al. proposed that EMM and SJS would be distinct disorders: EMM would consist of mucosal erosions and characteristic patterns of cutaneous lesions (typical targets, with or without blisters), symmetrical and preferably acral distribution, while SJS would be represented by mucosal erosions and widespread purpuric maculae, often confluent, with Nikolsky's sign positive and skin detachment limited to less than 10% of the body surface. EMM would include recurrent or post-infectious cases or those possibly related to exposure to drugs with low morbidity and no mortality. SJS, in turn, would constitute a most serious adverse drug-related disorder with significant mortality and poor outcome in many cases.[4,6]

Therefore, although TEN and SJS were historically considered part of a spectrum of disorders that included erythema multiforme major, as they all present with mucosal lesions clinically similar, these diseases are now considered apart. Since the extent of epidermal necrolysis is a major prognostic factor, it has become a consensus to classify the spectrum as follows: SJS, cases with skin involvement below 10%; SJS-TEN superposition, cases with

skin detachment between 10 and 30% of the body surface; and TEN, cases greater than 30%.[4,8]

Epidemiology

Statistics in Brazil are scarce in relation to its prevalence.[7] The literature suggests that SJS and TEN occur in approximately 2 to 3 people per million/year in Europe and the USA. The incidence of SJS specific ranges from 1.2 to 6 per million/year, with fatality in 5% of cases, while TEN affects 0.4 to 1.2 per million/year with mortality of 30% of patients.[2,7-9]

They can affect patients of all ages and races. TEN is more common in women, while SJS occurs more in the male population. Incidence increases with age and in certain risk groups[1] predisposing factors include: the existence of multiple comorbidities, polymedicated individuals, genetic susceptibility factors, immunosuppression (in HIV-positive patients, the risk is 1,000 times greater than in the general population), and concomitant use of radiotherapy and anticonvulsants.[1,2,4]

Pathophysiology

The pathophysiological mechanism is not fully understood. It is believed to be a delayed hypersensitivity reaction mediated by Th1 cells.

Some individuals have a genetic predisposition to develop such disorders: the so-called slow acetylators, deficient in enzymes involved in the destruction of toxic drug metabolites, such as glutathione transferase. Recently, genetic association of some HLA major histocompatibility complex alleles with the occurrence of serious drug reactions has been described.[1]

Histopathological hallmark of these diseases is widespread epidermal necrosis due to death by apoptosis of keratinocytes. CD8 cells act as mediators in this process. There are two pathways leading to apoptosis: the binding of Fas (CD95), a membrane receptor present in keratinocytes, with its FasL ligand (CD95L), and the release of the perforin and granzyme B pathways.[1,2,4]

Etiology

It is believed that drugs are the main cause of SJS (50 to 80% of cases) and TEN (around 80%), although these diseases can also be triggered by infections and malignancies.[1] The most common drugs are sulfonamides and penicillins (26%) and the most often associated infectious agent is herpes simplex virus (19.7%).[7]

While drugs and cancer are more associated with adult patients, infections are the leading cause in children: it is estimated that half of patients diagnosed with SJS had a recent upper respiratory tract infection.[7]

There are over 100 medications of various classes associated with the occurrence of SJS and TEN. In a recent international multicenter case-control study that included countries in Europe and Israel, the EuroSCAR (European Severe Cutaneous Adverse Reactions) trial, allopurinol was the most common cause of SJS and TEN, particularly when prescribed at doses equal to or higher than 200 mg per day. The following drugs were listed as the main ones related to the occurrence of SJS and TEN, based on RegisSCAR/EuroSCAR files.[1,10]

- High risk: allopurinol, carbamazepine, cotrimoxazole and other sulphonamides, sulfasalazine, lamotrigine, nevirapine, oxicam-derivative nonsteroidal anti-inflammatory drugs (e.g., meloxicam), phenobarbital, phenytoin;
- Moderate risk: cephalosporins, macrolides, quinolones, tetracyclines, acetic acid-derivative nonsteroidal anti-inflammatory drugs (e.g., diclofenac);
- Low risk: beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel inhibitors, thiazide diuretics, sulfonylurea antidiabetics, insulin, propionic acid-derivative nonsteroidal anti-inflammatory drugs (e.g., ibuprofen).

Analgesics include: paracetamol[11] and acetylsalicylic acid. It is important to note that in 2014, the Food and Drug Administration (FDA) required the manufacturers of acetaminophen (paracetamol) to include SJS risk warnings in the package insert. Dipyrone, by contrast, is not in the list of agents involved in the etiology of SJS; the possible association with SJS seems to stem from the concomitant use in infectious diseases whose etiological agents could be the real cause of the disease.

La Grenade et al., in a study of cases of SJS and TEN between 1969 and 2004, concluded that there is a significant risk of developing both drug reactions with sulfonamide derivative selective COX-2 inhibitors, particularly valdecoxib. With lower risk, but statistically significant, other COX-2 inhibitors such as celecoxib and rofecoxib, also correlated to these adverse reactions.[12]

The reported viral diseases include herpes simplex virus (HSV), HIV, coxsackievirus, influenza, hepatitis, lymphogranuloma venereum, and smallpox. Bacterial agents include group A beta-hemolytic streptococcus, the bacilli of diphtheria, brucellosis, typhoid fever and tularemia, mycobacteria and mycoplasma. Fungal causes include paracoccidioidomycosis, dermatophytosis and histoplasmosis. Protozoan parasites malaria and trichomonas were also related. In children, enteroviruses and Epstein-Barr virus are

possible causative agents. Carcinomas and lymphomas are also associated. Notwithstanding the different known etiologies, SJS is idiopathic in 25 to 50% of cases.[1,7]

Clinical picture

For most drugs triggering these reactions, there is an interval ranging from 4 to 28 days between the beginning of drug use and the onset of signs and symptoms. The highest risk of developing SJS and TEN occurs in the first 2 months of treatment with risk drugs on a continuous basis.

Both diseases can start with prodromal symptoms lasting up to 1 week, such as fever, sore throat, coughing, eye burning, myalgia and arthralgia. After this period there may be a discrete maculopapular rash, similar to a morbilliform rash.[1,4]

There may be atypical target lesions (with two instead of the three characteristic concentric rings found in EM) on the back of the hands, palms, sole of the foot, extensor surface of the limbs, neck, face, ears and perineum, with prominent involvement of trunk and face.[1,4]

The rash begins on the trunk with subsequent generalization, usually sparing the palmoplantar areas. Macular lesions become purplish, and epidermal detachment occurs, resulting in flaccid blisters that converge and break, resulting in extensive sloughing of necrotic skin (Figure 1). Nikolsky's sign is positive in perilesional skin.[1]

The difference between SJS and TEN would be the percentage of affected body area: cases involving less than 10% of the body would be classified as SJS, and those with over 30% of involvement would be TEN. Cases with involvement between 10 and 30% would be considered a superposition of the two entities.[4]

Mucosal involvement occurs in two or more distinct mucosal surfaces and may precede or follow the skin involvement. It begins with enanthem and edema that cause erosions and pseudomembranous formations in the eyes, mouth, genitals, throat and upper airways. About 10-30% of cases occur with fever and lesions in the gastrointestinal and respiratory tracts.[4]

Ocular involvement may be present in 39 to 61% of the cases presenting complications such as corneal ulcer, anterior uveitis, and panophthalmitis. Gastrointestinal adhesions, urinary incontinence, vaginal stenosis, renal tubular necrosis, renal failure, skin ulcerations with reinfection and non-esthetic scars are not uncommon.[7]

Loss of integrity of the skin barrier leads to increased chance of secondary bacterial infection, as well as disturbances in electrolyte balance and thermoregulation.[1]

Laboratory testing

There are no laboratory tests to point out the drug causing the disorder and, therefore, diagnosis is clinical.[13] A

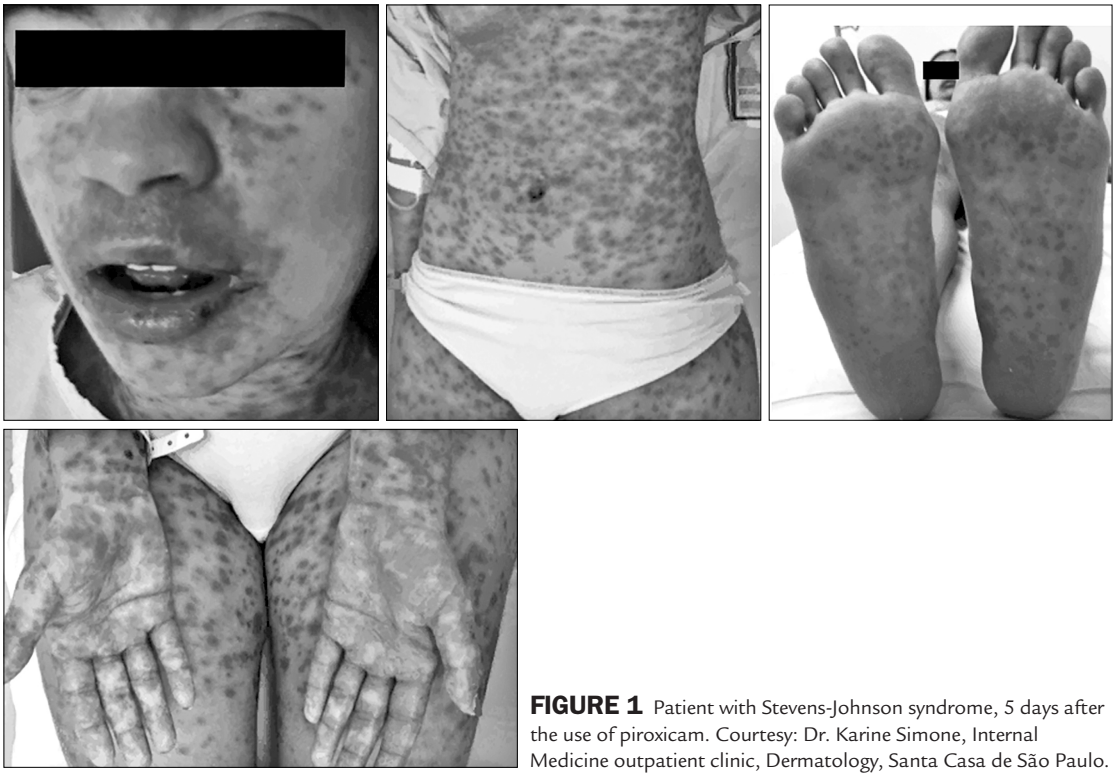

FIGURE 1 Patient with Stevens-Johnson syndrome, 5 days after the use of piroxicam. Courtesy: Dr. Karine Simone, Internal Medicine outpatient clinic, Dermatology, Santa Casa de São Paulo.

good history, with emphasis on the use of drugs and the occurrence of previous infections, and thorough physical examination are essential.

Drug provocation tests are contraindicated, since a subsequent exposure to the agent could trigger a new severe episode of SJS/TEN.[13]

Complete blood count (CBC) may show unspecific leukocytosis or even indicate superimposed secondary bacterial infection. Cultures of blood, urine and skin may reveal the agent of the underlying suspected infection.[13]

Skin biopsy is an additional final examination and reveals necrosis in all layers of the epidermis caused by apoptosis of keratinocytes and epidermal detachment, while the dermis displays minimum inflammatory changes[1] (Figure 2).

Serum levels of tumor necrosis factor-alpha and soluble Il-2, Il-6 and C-reactive protein receptors are typically elevated in patients with SJS, although none of these serological tests are used routinely for diagnosis in our midst.

Differential diagnosis

The most important differential diagnoses include disorders involving the peeling of the skin, such as erythema multiforme major, herpes simplex virus (HSV)–associated erythema multiforme, burns, widespread fixed drug eruption, acute generalized exanthematous pustulosis, erythroderma, bullous pemphigoid, linear IgA dermatosis, paraneoplastic pemphigus, lymphoma, angioimmunoblastic lymphadenopathy, viral rashes, secondary syphilis, herpetic gingivostomatitis, staphylococcal scalded skin syndrome, graft *versus* host disease and autoimmune vasculitis.[1-3,13]

Treatment

Management of patients with SJS or TEN requires three measures: removal of the offending drug, particularly drugs known to be high-risk; supportive measures and active interventions.

Early diagnosis of the disease, recognition of the causal agent and the immediate withdrawal of the drug are the most important actions, as the course of the disease is often rapid and fatal.

Figuring out the offending drug may not be easy and, in these cases, all drugs non-essential to the maintenance of the patient's life should be suspended.

Support treatment

Patients should preferably be treated in burn units. The first care should include supportive and symptomatic measures: body temperature control, hydration and electrolyte replacement, special attention to the airways, preventing secondary infection, pain control, maintenance of venous access distant from the affected areas, early oral nutrition or parenteral nutrition, if necessary, and anticoagulation.[7,14]

Skin lesions are treated according to the protocol for patients with large burns. There is no consensus on topical care. Topical antiseptics can be used, or just soap and water, in quick baths.[7]

The practice of debridement is controversial.

Prophylactic antibiotic therapy is not recommended as it can induce resistance and because these drugs can *per se* be causative agents of SJS or TEN. Therefore, they are given only in proven cases of infection, or when there is sudden decrease/rise in temperature, poor general condition, or positive skin cultures.[14]

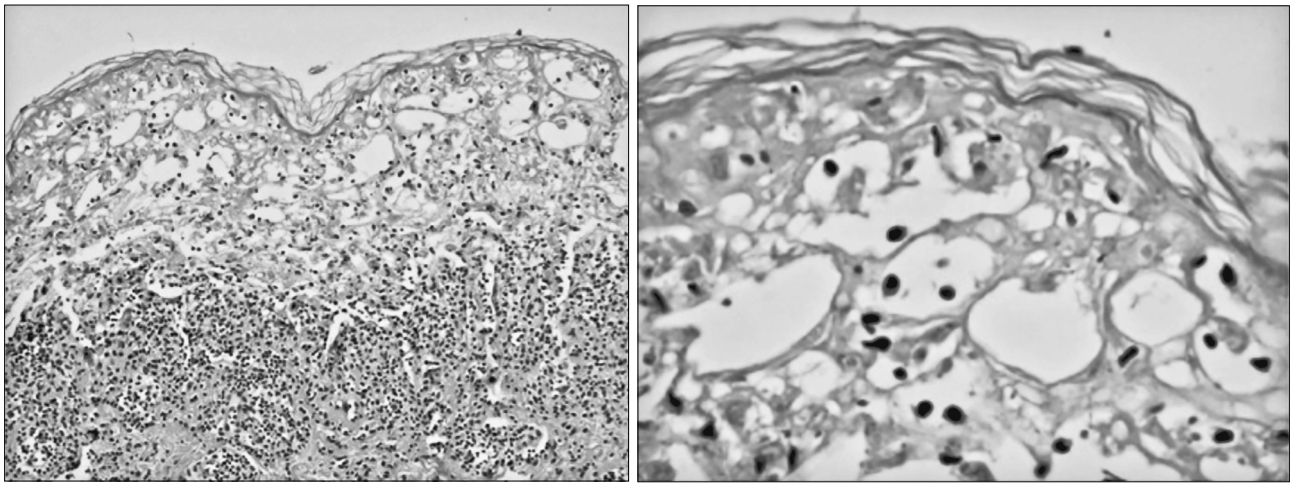

FIGURE 2 Pathological examination of the skin of a patient with Stevens-Johnson syndrome.

Ocular sequelae require daily examinations by an ophthalmologist.

Active interventions

Specific therapies for SJS and TEN have not yet reached evidence-based acceptance standards. The low prevalence of the disease and its lethal potential make it difficult to perform randomized clinical trials.

Some reviews concluded that steroids do not shorten the duration of disease and may also increase the risk of infections and worsen healing. Many authors do not recommend the routine use of systemic steroids in the treatment of SJS/TEN but some centers advocate an early pulse (first 48 hours).[13-17]

Studies have suggested benefit of plasmapheresis for the treatment of SJS/TEN; however, there are reports showing that its use did not significantly affect mortality and length of hospital stay in some cases.[13-17]

Cyclosporin is an immunosuppressive medication with anti-apoptotic activity and has been considered as a potentially useful drug for treatment; however, its usefulness is not well defined.[13-17]

Viard et al., in 1998, reported that commercial preparations of intravenous immunoglobulin contained natural anti-Fas (anti-CD95) antibodies that blocked Fas to FasL binding, thus intervening in disease pathogenesis. The studies show mixed results. Successful treatment depends on the dose and its early use.[13-17]

Prognosis

Prognosis is linked to rapid identification of the causative drug and its discontinuation. It is crucial to quickly establish proper clinical diagnosis, so that the causative drug may be discontinued and appropriate treatment initiated.

In SJS, the mortality rate is typically less than 5%, and sepsis is the main cause of death. Prognosis does not seem to be affected by the type or the dose of the causative drug, or by HIV infection.

A score called SCORTEN developed by Bastuji-Garin et al. determines the variables as predictors of prognosis and risk of death in patients with SJS and TEN.[18]

In addition to the SCORTEN predictors, other factors determinant of poor prognosis include late withdrawal of the causative drug and delay to transfer the patient to an aseptic or burn unit.

Resumo

Síndrome de Stevens-Johnson e necrólise epidérmica tóxica: revisão

A síndrome de Stevens-Johnson (SSJ) e a necrólise epidérmica tóxica (NET) são doenças mucocutâneas pouco frequentes, agudas e potencialmente ameaçadoras à vida. Representam uma reação de hipersensibilidade e podem ser desencadeadas por fármacos, infecções e neoplasias. Dentre os principais medicamentos descritos como causadores do quadro estão o alopurinol, alguns antibióticos do grupo das sulfonamidas, anticonvulsivantes, como carbamazepina, e alguns anti-inflamatórios não esteroidais. A necrose dos queratinócitos manifesta-se clinicamente pelo descolamento epidérmico, levando a um aspecto de pele escaldada. A erupção inicia-se no tronco, com posterior generalização, geralmente poupando as áreas palmoplantares. As máculas tornam-se violáceas e há descolamento epidérmico, dando origem a bolhas flácidas, que confluem e se rompem, deixando áreas extensas erosadas. A pele perilesional apresenta sinal de Nikolsky positivo. A SSJ e a NET representam espectros da mesma doença, diferenciando-se pelo grau de descolamento epidérmico. O tratamento da SSJ e da NET é fundamentado em três medidas: retirada da droga ofensora, especialmente as medicações conhecidamente de alto risco; medidas de suporte e intervenções ativas. O diagnóstico precoce da entidade, o reconhecimento do agente causal e a retirada imediata do fármaco são as mais importantes ações, visto que a evolução dos casos é muitas vezes rápida e fatal.

Palavras-chave: síndrome de Stevens-Johnson, necrólise epidérmica tóxica, erupção por droga.

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