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Review Article

Stevens-Johnson syndrome and toxic epidermal necrolysis: a review

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ABSTRACT

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are considered a single entity with variability in the extent of the lesions, characterized by erythema multiforme that may involve mucosa. Severe cutaneous reactions secondary to medications are classified according to the area of epidermal detachment. The activation of cytotoxic T cells and macrophages is mediated mainly by IL-2 and interferon gamma secreted by Th1 lymphocytes, and the activation of eosinophils and B lymphocytes in IgE is mediated by secreted IL-4, IL-5, IL-10 and IL13 by B lymphocytes. The topography of SJS is predominantly central, affecting the trunk and sometimes a generalized dissemination is shown that affects a body surface area of less than 10%, characterized by irregular violaceous erythematous macules of target shooting, which can form confluent blisters. TEN is characterized by a skin detachment greater than 30% of the body surface, whose predominant lesion is diffuse erythema with individual macules, which give rise to detachment surfaces greater than 5 cm. The treatment is symptomatic, nonspecific, and aimed at avoiding complications, carried out in specialized intensive care units, due to ignorance of the pathogenesis. Integral management with different therapeutic alternatives can represent a crucial part in the multisystemic management of SJS and TEN.

Keywords: Blisters, Complications, Drugs, Erythema, Mucous membranes, SJS, Skin rash, TEN

INTRODUCTION

Stevens Johnson syndrome (SJS) was first described in the year 1922 by doctors AM Stevens and FC Johnson as a generalized skin rash, which can affect mucous and with the presence of fever, just 34 years later Lyell A, described four clinical cases of patients with erythema and blisters, caused by a toxin responsible for epidermal necrosis (TEN).[1,2] Currently Stevens Johnson Syndrome and toxic epidermal necrolysis are considered a single entity with variability in the extent of the lesions, characterized by erythema multiforme that may involve mucosa.[3]

Severe cutaneous reactions secondary to medications are classified according to the area of epidermal detachment. The spectrum is represented in Table 1, with toxic epidermal necrolysis being the largest cutaneous extension.[4]

Table 1: Comparison between SJS and TEN.

	Genes Involved (alleles)	Skin Affectation	Adult Incidence	Mortality	Diagnosis (Clinical Presentation)	Treatment
SJS	2, 15, 38, 59	<10%	9.2 per million	4.8%	Central location of violaceous erythema with confluent blisters.	Palliative Care Topical and systematic treatment
SJS/TEN	2, 15, 38, 59	10-30%	1.6 per million	19.4%	On position of the two clinical forms	Palliative Care Topical and systematic treatment
TEN	29, 73	>30%	1.9 per million	14.8%	Diffuse erythema with isolated macules, with large areas of detachment	Palliative Care Topical and systematic treatment

REVIEW OF LITRATURE

Etiology

Although the etiology is varied, 80-95% of cases are due to the use of drugs.[5] A smaller number of cases have an idiopathic etiology, which is more common in children.[6] Sassolas B et al, Developed a standardized algorithm to establish the causal relationship between drugs and SJS/TEN based on 6 parameters, the time from the ingestion of the drug and the start of the reaction, the probability of presence of drugs in the body on the initial day, previous history of adverse reaction to the same drug, the presence of the drug during the progression of the disease, previous evidence of the drug based on previous results of SCAR, and the presence or absence of other etiological causes. In all of these categories, positive or negative values are assigned that make the scale more reliable.

The results are classified as very probable, probable, possible, improbable, and very unlikely; a relationship has been established with the following drugs through the application of the ALDEN score: allopurinol (odds ratio 24.51), cox-2 inhibitors (odds ratio 24.19) PPI, fluoxetine, mirtazapine, 5-aminosalicylates, lamotrigine, Nevirapine, phenobarbital, phenytoin and sulfamethoxazole.[7,8,4]

Genetically, hypersensitivity reactions and variants of HLA have been associated, which are specific for populations and drugs, which indicates that these specific HLA interact closely with molecules that act as antigens in drugs, causing the activation of T cells.[9] The presence of the allele HLA-B* 1502 is related to a greater predisposition to cutaneous hypersensitivity reactions secondary to the use of carbamazepine in Asian populations and to the HLA-A* 3101 allele in North European populations.[10,11]

Physiopathology

The activation of cytotoxic T cells and macrophages is mediated mainly by IL-2 and interferon gamma secreted by Th1 lymphocytes, and the activation of eosinophils and B lymphocytes in IgE is mediated by secreted IL-4, IL-5, IL-10 and IL13 by B lymphocytes[5]. Activated in turn by the drug. Activated cytotoxic cells degranulate cytotoxic proteins such as granulisin, perforin, granzyme B and Fas ligand. The identification of high amounts of granulisin in the content of the vesicles, has thus demonstrated that it is the main cytotoxic molecule, responsible for the death of keratinocytes.[12] Granulisin interacts with lipids similar to saposin, this characteristic confers bactericidal and cytolytic activity, permeabilizing the mitochondrial and lysosomal membrane, thus triggering cell death due to the loss of homeostasis with subsequent release of cytochrome C and apoptosis-inducing factor.

It also has the ability to recruit chemokines such as CCL3, CCL5, MCP-1, MCP -3 and cytokines such as IL-1, IL-6 and IFN-α. The amount of perforin and granzyme B is related to the severity of the disease and also the inhibition of these decreases its cytotoxic effect, although its mechanism is not well described, most theories agree on the perforin cytolytic effect that allows the Granzyme B accesses the cytosol, where it can cut and activate caspases or activate independent caspase pathways when generating reactive oxygen species. The origin of Fas L is not completely known, although it is well described that the binding of Fas with its ligand causes the coupling of the receptor and the transduction of an apoptotic signal, in addition to the activation of NF-κB and giving way to inflammation. Numerous cytosines play important roles such as vascular endothelial permeability and cellular activation and differentiation is given by TNFα released by macrophages and keratinocytes, in addition to the participation of IFN-γ and numerous interleukins.[13]

Epidemiology

The estimated average incidence in the EU for 2016 of SJS was 9.2, SJS/TEN 1.6 and TEN 1.9 per million adults. Hsu D estimate the average annual mortality rate adjusted for age and sex in the US of 4.8% for SJS, 19.4% for SJS/TEN and 14.8 for TEN. Factors such as advanced age, associated chronic diseases, infections and malignant neoplasms increase the risk of mortality.[14]

Given the suspicion of a drug reaction accompanied by blisters and erosions, withdrawing medications improves the prognosis and reduces mortality.[15]

In the General Hospital of Mexico, a retrospective study was carried out, finding acute reactions to medications as the third cause of mortality (14%), with infections and hydroelectrolytic imbalances being the main complications.[16]

During 2013 dermatological diseases occupied the first place in years of life lost due to illness, although the SJS or TEN are not among these, it is a potential cause of mortality.[16,17] Currently the SCORTEN scale (SCORE of Toxic Epidermal Necrolysis) is used to predict mortality, consists of 7 parameters, of which only three (heart rate, blood urea and serum bicarbonate) appear to be significant in different populations , probably due to the demographic variability of them.[18]

Clinical presentation

Skin manifestations are preceded by 1 to 3 days by nonspecific symptoms such as pain in mucous membranes, headache, malaise and myalgias.[19]

The Nikolsky sign is positive in any variant of the spectrum, is described as direct when the pressure of the fingers on the skin is sufficient to remove the epidermis, and indirectly when pressure is exerted on the blister with the fingers.[3]

This sign is also present in some cases of burns, ichthyosiform bullous erythroderma, scalded skin syndrome and pemphigus, although the pathological process is different.[20]

In 2014 a 5 year retrospective study showed that the average age of presentation was 49.5 years, with an average evolution of the clinical picture of 3.6 days, the main sign being reported being erythema, present in 53.3% of patients, followed by of fever, oral ulcers, edema, ocular symptoms and myalgias, of the 43 patients studied, 97.7% showed involvement of the oral mucosa, predominantly in patients with SJS, 88.4% ocular involvement, predominantly in patients with TEN, 55.8% presented involvement of the genital mucosa with predominance in patients with TEN, 48.8%. presented hepatitis, predominant in patients with SJS/TEN, and 23.2% presented microscopic hematuria predominantly in patients with TEN.[21] Figure 1.

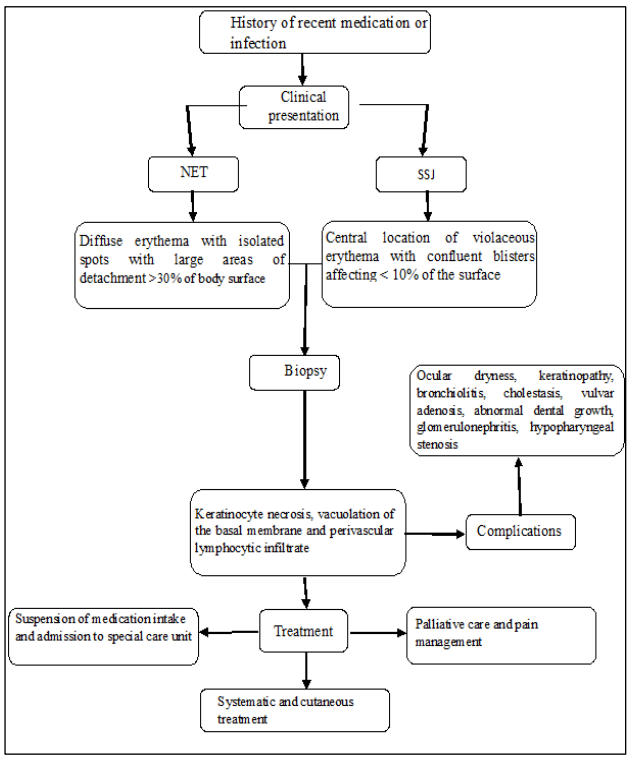

Figure 1: Stevens Johnson syndrome and TEN.

The topography of SJS is predominantly central, affecting the trunk and sometimes a generalized dissemination is shown that affects a body surface area of less than 10%, characterized by irregular violaceous erythematous macules of target shooting, which can form confluent blisters. TEN is characterized by a skin detachment greater than 30% of the body surface, whose predominant lesion is diffuse erythema with individual macules, which give rise to detachment surfaces greater than 5cm.[19] And the spectrum that affects 10% to 30% of the skin is called SJS/TEN.[22]

Diagnosis

The diagnosis is made from the clinical presentation and the histological characteristics of the lesions. The degree of affectation of the corporal surface is understood as the total or partial detachment of the epidermis, the erythematous or violaceous lesions that do not detach are not contemplated in the degree of affectation.[23] Considering the histopathological characteristics, SJS and TEN share the characteristic pattern with Erythema Multiforme (EM), the latter being differentiated by its clinical presentation of multiform eruption or target shooting.

The main findings include extensive or complete dissemination of necrotic keratinocytes. The formation of subdermal blisters is due to vacuolization at the level of

the basement membrane. In addition, a superficial perivascular lymphocytic infiltrate can be found.[3]

Treatment

The treatment is symptomatic, nonspecific, and aimed at avoiding complications, carried out in specialized intensive care units, due to ignorance of the pathogenesis.[19] There are two types of treatments used, systemic and palliative treatment Table 2.

The therapeutic alternatives used in this syndrome are shown below:

Systemic treatment

• *Corticosteroids*

They are the oldest treatment that exists for TWN. In the literature there is disagreement between the results of patients treated with corticosteroids, these differences may be due to the variation in the dose administered, duration, and time of evolution of the clinical picture in which it was administered.[24] A Third-level pediatric hospital in Thailand reported that despite being corticosteroids the treatment of choice to reduce excessive immune response, their retrospective study at 20 years did not find an increase in the efficacy of use with corticosteroids and symptomatic treatment [25]. Concluding that the administration of corticosteroids is not recommended as a single therapy in cases of SJJ and TEN. [26]

• *Intravenous immunoglobulins*

The efficacy of IV Ig treatment is based on the theory that these reduce the concentration of Fas, therefore decreasing keratinocyte necrosis Table 3.

Table 2: Topical and palliative treatment for SJS/TEN.

Type of treatment	Treatment
Palliative	1. Temperature from 30 to 32 °C
	2. Rest on an alternate pressure mattress
	3. Replacement of electrolytes, liquids and albumin, approximately 2/3 to 3/4 of replacement
	4. If necessary, gastrointestinal support for feeding
	5. Analgesics in case of pain
	6. Suspected Infection
Topical	1. Puncture ampoules or extreme care to avoid bursting
	2. The denuded surfaces should be coated with gauze soaked in antiseptic solutions
	3. If there are allografts or dermal coverage, debride the lesions under anesthesia
	4. Mucosal lesions should be evaluated and treated by specialists (urology, ophtalmology)
	5. Oral mucosal lesions treated mouthwash and ointments that help reepithelialization as panthenol

Table 3: IV treatment.

Name	Mechanism of action	Dose	Adverse effects	Contraindication
Dexamethasone	Corticosteroid that inhibits inflamatory cytokines	8-16 mg/day for 7-10 days	Hypertension, Cushing syndrome, vision alterations	Ocular infection, glaucoma, use of rilpivirine
IV Ig Inmuno-globulins	Interferes with death induced by ligand apoptosis	1-2 g/kg/day for 3 days	Hypertension, hypotension, pruritus, increased body temperature, ulcers, diarrhea	Fructose intolerance, hyperprolinemia, IgA deficiency
Cyclosporine	Inmunomodulator with specific target in granulokin (mediator of apoptosis in keratinocytes)	3- 5g/kg/day for 7 days	Hirsutism, pruritus, abdominal pain, triglyceride elevation, diarrhea, headache	Use of PUVA or UVB, use of methotrexate, abnormal renal function
Thalidomide	(Anti-TNF) Not known	50-200 mg for 3-6 months	Edema, dry skin, hipocalcemia, constipation, leukopenia, high mortality	Neutrophil countless tan 750/mm
Etanercept	It binds to TNF alpha and TNF beta, making TNF biologically inactive	12 weeks- 3 months	Psoriasis at the site of application, respiratory tract infection, congestive heart failure, multiform erythema	Sepsis
Plasmapheresis		3 a 8 sessions	Paresthesia, hypotension, and allergic reactions	

- *Anti-TNF*

TNF-α participates in the pathology of TEN, a randomized double-blind controlled study was developed that will evaluate the effect of thalidomide, which could not be terminated due to the high mortality of the study. Due to the same, thalidomide is contraindicated in these patients, not so Infliximab and etanercept, which showed beneficial effects.

• *Cyclosporine*

It is recommended at an average dose of 3-5 g/kg/ day for 7 days for treatment in the case of TEN due to a reduction in the predicted mortality according to the SCORTEN scale, a decrease in the time of hospitalization and in the duration of re-epithelialization of mucous membranes, besides showing few adverse effects.

• *Plasmapheresis*

The results of this treatment have been mentioned in numerous case reports, which opt for 3 to 8 sessions of this treatment after not obtaining the desired results with corticosteroids and IVIG, which until now are safe and without severe adverse effects. Adverse reactions are usually paresthesia, low blood pressure, and allergic reactions.

• *N-acetylcysteine*

Administered intravenously as a glutathione precursor, which increases the detoxification of drugs and inhibits the production of inflammatory cytokines. Recent studies show an increase in predicted mortality, and its use with anti-TNF can, contrary to what was thought, diminish its effect.[24]

DISCUSSION

Although most of the complications are ocular, there is documentation of complications in different locations such as:

- Eyepieces: Ocular dryness, loss of palisades of Vogt., Superficial keratopathy, abnormalities in the mucocutaneous junction, conjunctival hyperemia, trichiasis.
- Respiratory: Bronchiolitis obliterans, acute and chronic, bronchiectasis
- Gastrointestinal.-Stenosis and esophageal networks, obstructions of the small intestine, intestinal ulcers
- Hepatic: Chronic cholestasis and ischemic hepatitis
- Gynecological: vulvar and vaginal adenosis, vaginal stenosis, fusion of labia minora and minor, hematocolpos and hydrocolpos
- Oral: abnormal dental growth, labial synechia
- Laryngeal otorhinogen: hypophogeal stenosis, synechiae in the nasal septum, stenosis of the auditory canal
- Renal: Glomerulonmephritis.[27]

Prevention of complications

- Eyepieces: Administration of artificial tears, removal of pseudo-membranes, blepharoplasty, debridement of detached epithelium, antibiotics and topical corticosteroids.
- Oropharyngeal: Use of antiseptic or antifungal solutions for washing the oral cavity.
- Genital: Baths and lubrication with emollients in order to reduce secondary constrictions to erosions, intravaginal steroids, vaginal molds until checking the healing of the vaginal mucosal lesions, and suppression of menstruation, thus avoiding the risk of vaginal adenosis.[19]

CONCLUSION

SJS and TEN are part of the same spectrum of the disease, with nonspecific clinical manifestations and main characterization factors due to the extent and severity of the skin lesions. Integral management with different therapeutic alternatives can represent a crucial part in the multisystemic management of SJS and TEN. Most of the complications must be referred and resolved by their respective specialist, but there are prevention measures for the most common complications among which are highlighted.

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