International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 12 December 2023

Page No: 3123-3128

DOI: https://doi.org/10.47191/ijmscrs/v3-i12-36, Impact Factor: 6.597

Toxic Epidermal Necrolysis Induced by Allopurinol, One Case in A Million

Lucero Carmen León Rocha [1], Sarahí Elizabeth Rodea Montellano [2], María del Rosario Escalona Arroyo [3], Ángel Ramiro García Navarro [4], Martha Méndez Carrasco [5], Jahir Fresnel Narcisse Alvarez [6]

[1]Hospital General de Zona 2ª, "Francisco del Paso y Troncoso", IMSS.

[2]Hospital de Especialidades "Bernardo Sepúlveda", Centro Médico Nacional Siglo XXI, IMSS.

[3]Hospital Regional "General Ignacio Zaragoza"

[4]Hospital Regional Dr. Valentín Gómez Farías.

[5]Unidad de Medicina Familiar 21 Instituto Mexicano del Seguro Social.

[6]Hospital de Especialidades Dr. Bernardo Sepúlveda Gutiérrez CMN Siglo XXI

ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are part of the spectrum of one of the most serious dermatological conditions that occur in the hospital setting, considered a dermatological emergency. Stevens-Johnson syndrome is called toxic epidermal necrolysis (TEN) when ≥30% of the body surface is affected, and it is the most serious form of the disease, with adverse drug reactions being the main etiology, up to 80%.

Clinical case: We present the clinical case of a 30-year-old male, with a history of systemic arterial hypertension, who began with symptoms after taking allopurinol after being diagnosed with hyperuricemia. It began with a picture of bilateral conjunctivitis, followed by a sudden appearance of localized dermatosis on the face, characterized by erythematous plaques with indistinct, non-painful borders, and later the appearance of ulcers and blisters, extending to 70% of the body surface. During his hospitalization, he developed a lesion acute renal failure, managed by the intensive care service, with total remission upon discharge and favorable response to treatment thanks to multidisciplinary management. Treatment was provided with human immunoglobulin, vancomycin-based antibiotic therapy, and ciprofloxacin for impetiginization of facial ulcers, fluid therapy, Vaseline gauze dressings, and topical ophthalmological treatment, achieving discharge without comorbidities.

Conclusion: Toxic epidermal necrolysis is a severe picture of Steven Johnson Syndrome, potentially fatal, which requires early multidisciplinary management that leads to the recognition and management of associated comorbidities in a timely manner.

KEYWORDS: Stevens-Johnson syndrome; toxic epidermal necrolysis; halopurinol, drug reaction.

ARTICLE DETAILS

Published On:
19 December 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are part of the spectrum of one of the most severe dermatological conditions that occur in a hospital setting.[1] Toxic Epidermal Necrolysis (TEN) is a variant presentation of Stevens-Johnson Syndrome (SJS, involving < 10% of affected skin). Lyell syndrome (also known as Toxic Epidermal Necrolysis, TEN, is termed when ≥ 30% of the skin is affected), and it is called an overlap syndrome when 10 to 29% of the skin is affected.[2,3] This spectrum of diseases is characterized by cytokine-mediated keratinocyte apoptosis, resulting in the separation of the dermal-epidermal junction and extensive detachment of the necrotic epidermis.2,4 The incidence of SJS/TEN varies from 1.4 to 9.2 cases per million people per year. However, it represents an entity with high mortality ranging from 20 to 25% during the acute phase and 30 to 35% at 1 year.[3,5,6].

SJS/TEN presents with erythematous or violaceous patches, atypical targetoid lesions, blisters, erosions, and ulcers. Blisters usually exhibit a positive Nikolsky sign, and the distinctive feature of SJS/TEN is mucosal involvement (present in 80% of cases), with oral sites more commonly affected than ocular, genital, or anal mucosa. Systemic symptoms may also be present and may precede cutaneous involvement.[1,3,4]

SJS/TEN primarily result from an idiosyncratic reaction to drugs (more than 80% of cases). Anticonvulsants account for 50% of cases; non-steroidal anti-inflammatory drugs, 33%; antibiotics, 34-80% (sulfas, beta-lactams, and quinolones); antiretrovirals (especially nevirapine) and allopurinol are also significant causes.[4,7]

The management of this disease with extensive involvement exceeding 10% of the total body surface area requires a specialized intensive care unit (ICU) for critical care management and specialized nursing.[2] The multidisciplinary team in the treatment of SJS/TEN should be coordinated by a cutaneous failure specialist, usually in dermatology and/or plastic surgery, and should include intensive care physicians, ophthalmology, and specialized skin care nursing.[4]

AIM

To present the case of a 30-year-old male patient who developed TEN after ingesting allopurinol, a medication rarely associated with this condition, highlighting the importance of comprehensive treatment.

CLINICAL CASE

A 30-year-old male with a history of systemic arterial hypertension diagnosed and treated with bisoprolol 5 mg every 24 hours for the past 2 months and recent diagnosis of hyperuricemia treated with allopurinol 300 mg every 24 hours for the last 20 days prior to hospital admission.

His symptoms began three weeks after the initiation of the medication, starting with bilateral conjunctival hyperemia and a sudden appearance of dermatosis on the face characterized by non-painful, poorly defined erythematous plaques. It later progressed to ulcers and blisters, covering 70% of the body surface, along with extensive areas of erythematous-desquamative plaques, associated with ulcers in the oral mucosa and purulent conjunctivitis. Fig,1,2,3.

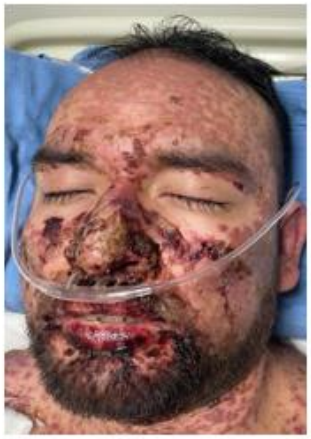

Fig 1 Mucosa affected

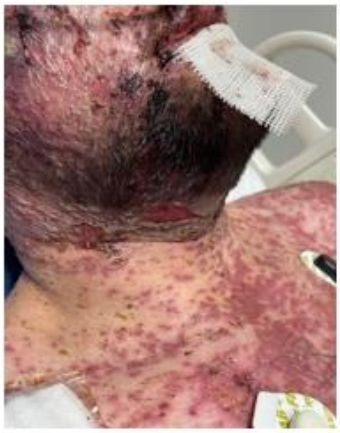

Fig 2. Extension of lesions: Purplish spots with blisters that tend to coalesce + denuded

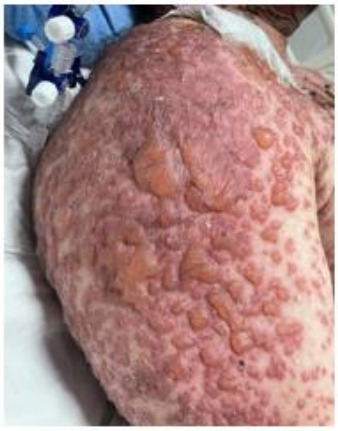

Fig 3 Floppy blisters on chest and right arm (Bullous impetigo).

Evaluated by the emergency department, he was admitted to the internal medicine floor where he met clinical criteria for a NET diagnosis, with an affected area exceeding 30% of the total body surface, mucosal involvement, and a history of drug intake associated with characteristic dermatosis. Fig 4,5

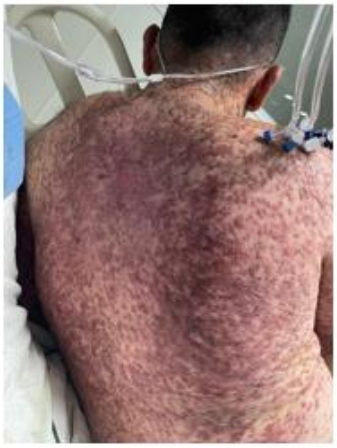

Fig 4. Epidermal detachment in neck

Fig 5. Dermatosis with extension to anterior chest

During his stay in the internal medicine service, there was a torpid evolution with the addition of acute kidney injury and progression of the dermatosis in extension, leading to management by the Intensive Care Unit. Medical treatment was initiated with intravenous fluid therapy, based on calculations for a major burn patient. Careful debridement of necrotic areas was performed, followed by coverage with petrolatum gauze in pus-filled blister areas. Careful debridement and subsequent application of silver sulfadiazine were done in areas of epidermal necrosis. For the affected oral mucosa, mouthwashes with Philadelphia solution were used (5 ml 1% lidocaine, 30 ml aluminum and magnesium hydroxide gel, 30 ml chlorpheniramine syrup, or 30 ml diphenhydramine syrup).[10]

In the ocular region, chloramphenicol eye drops, accompanied by lubricating eye drops, were used to prevent corneal ulcers and complications. Later, intravenous immunoglobulin treatment was added (3 doses, calculated at 1 mg/kg), and antibiotic therapy due to a superimposed infection in facial ulcers, showing purulent material, increased pain, edema, and erythema in the affected areas. Empirical antibiotic therapy was initiated with vancomycin 1g every 12 hours for 7 days, ciprofloxacin 400 mg IV every 12 hours for 7 days, with an adequate response, resolution of infection signs, and subsequently no evidence of systemic inflammatory response.

A multidisciplinary approach in collaboration with the Intensive Care, Dermatology, Ophthalmology, and Infectious Diseases services was provided. The patient gradually showed favorable clinical evolution, resolution of acute kidney injury, and improvement of the associated dermatosis. Subsequently, widespread reepithelialization was observed, improvement in laboratory parameters, absence of systemic inflammatory response or coexisting infection, and no evidence of associated sequelae or long-term complications. He was discharged from the intensive care unit and admitted to the internal medicine service where he continued to progress favorably.

After 14 days of hospitalization, he was discharged home without associated sequelae or comorbidities, with a 90% improvement in dermatosis. Follow-up in the outpatient clinic showed complete remission of dermatosis with residual hyperchromic spots, no associated scars or long-term complications. Follow-up appointments at 3, 6 months, and 1 year included laboratory studies, all of which showed biochemical parameters within normal ranges, and complete and adequate healing of the affected dermal lesions. Fig 6,7,8.

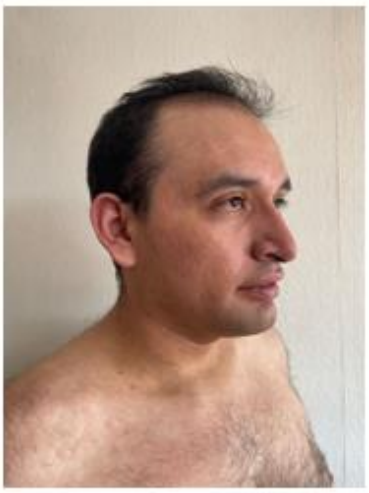

Fig 6. 3 months after hospital discharge

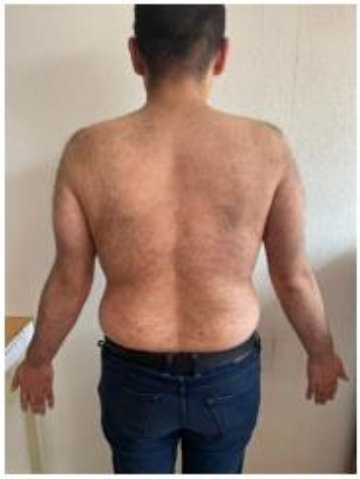

Fig 7. Posterior region of thorax, without visible scars

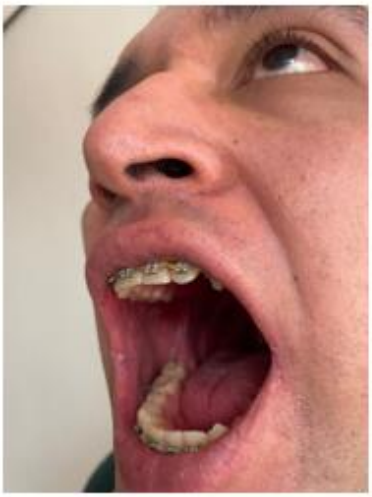

Fig 8. Oral mucosa with adequate healing, no sequelae are perceived

DISCUSSION

Toxic Epidermal Necrolysis (TEN) is a clinical variant of the presentation of Stevens-Johnson Syndrome (SJS); however, the difference between the two lies in the degree of total body surface area involvement. While SJS affects <10% of the total body surface area, TEN affects >30% of the surface. There is also a clinical presentation variant known as overlap syndrome, where 10 to 29% of the total body surface area is affected.

These rare diseases are triggered, in 80% of cases, by pharmacological treatments,[3,4,5] presenting symptoms between 4 and 28 days after the start of treatment. Mortality during the acute phase is 20 to 25%, and a significant number of patients experience disabling sequelae (mainly ocular impairment and psychological distress).[5]

The most frequently reported etiology in the literature attributes these reactions to drugs, including allopurinol, carbamazepine, phenytoin, lamotrigine, phenobarbital, cotrimoxazole, and other anti-infective sulfonamides, sulfasalazine, non-steroidal anti-inflammatory drugs

(NSAIDs), oxicam, and nevirapine. As mentioned previously, an environmental factor caused by Mycoplasma pneumoniae and viruses [3,4,5,10,] is also described. In our clinical case, the patient presented symptoms approximately 20 days after taking allopurinol.

Pathogenesis: Three causative pathogenic mechanisms for drug reactions are considered: immunologic mechanisms, non-immunologic mechanisms, and idiosyncratic mechanisms. In the case of SJS and TEN, the causal mechanism is adaptive immune, involving delayed hypersensitivity IV response. The immune mechanism causing SJS and TEN is a delayed cellular response leading to keratinocyte apoptosis. Two theories have been proposed as the mechanism of action. The first involves the FAS-FASL (Fas ligand) signaling pathway, activating caspase 8, inducing keratinocyte apoptosis.[12] The second, more widely accepted, suggests that cell apoptosis is caused by cytotoxic T lymphocytes (CD8) and natural killer cells (NK) following activation by the drug. The drug becomes immunogenic after binding to a peptide, stimulating the immune system. Keratinocyte apoptosis is caused by a 15 kDa cytolytic protein called granulysin, present in the granules of CD8 T lymphocytes and NK cells. In our case, the patient's clinical presentation aligns with a latency of approximately 20 days from allopurinol ingestion.[12,13]

Clinical Presentation: Initial skin involvement sites are the presternal region of the trunk, face, and proximal parts of the extremities. The characteristic dermatosis consists of dark red, irregularly shaped purpuric macules, progressing to vesicles and bullae with a necrotic center. Mucosal involvement is observed in over 80% of cases, affecting at least two sites and may be inaugural in a third of cases. Painful inflammation and erosions occur in the mucous membranes, typically starting with burning pain and paresthesias in lips, conjunctivae, and genitals. Ocular involvement, such as conjunctival inflammation, was observed in our patient. The percentage of epidermis detached classifies patients into three groups: SJS (<10%), SJS/TEN overlap (10-30%), and TEN (>30%). [1,3,5]

Multisystem Failure: SJS/TEN corresponds to acute cutaneous failure associated with severe weakness, intense pain, and prolonged high fever. Internal epithelial organ dysfunction is rare and mainly affects the respiratory and gastrointestinal tracts. Renal involvement, observed in the acute phase, is primarily represented by acute renal failure, proximal acute tubular necrosis, hematuria, and microalbuminemia. Fortunately, our patient only presented acute kidney injury as an associated comorbidity, which resolved with conservative management.[2,3]

DIAGNOSIS

Diagnosis is essentially clinical, considering the characteristic features, intense pain, high fever, mucosal involvement, purpuric macules progressing to vesicles and bullae Fig 3, positive Nikolsky sign, widespread dermatosis, and a direct relationship with a drug history. Clinical criteria help standardize medical action for greater diagnostic precision. Our patient met all clinical criteria, leading to admission to the internal medicine service and subsequent admission to the ICU for management. [3]

PATHOLOGY EXAMINATION

A skin biopsy with pathological examination and direct immunofluorescence analysis is required to confirm the diagnosis and rule out other blistering diseases with a similar clinical presentation (such as linear IgA dermatosis)[5]. If clinical data are clear and in areas where biopsy is not feasible, diagnosis can be made without the need for biopsy. Histological findings are characterized by nests of apoptotic keratinocytes with subsequent necrosis of the entire thickness of the epidermis and a dermal infiltrate consisting predominantly of lymphocytes.[5]

TREATMENT

Immediate cessation of any suspected medication is the cornerstone of TEN treatment. [8,11] Early recognition and appropriate management can save lives. However, there are no internationally accepted management guidelines. The initial diagnosis and evaluation of the patient in the acute phase require multidisciplinary cooperation within a highly specialized center, involving specialists from various areas such as dermatologists, intensivists, plastic surgeons, pediatricians, pulmonologists, infectious disease specialists, ophthalmologists, otolaryngologists, stomatologists, gynecologists, urologists, gastroenterologists, psychiatrists, psychologists, nutritionists, nurses, and social workers [5,8]. In our patient's case, despite being a second-level facility without sufficient specialized areas or personnel, a multidisciplinary effort was made to achieve comprehensive treatment with the available specialists.

In the literature review, we found a protocol that served as a basis for establishing useful treatment guidelines:

1. Identification and withdrawal of the culprit drug and all non-essential medications.[3,11]
2. Transfer of the patient to intensive care, burn unit, or another specialized unit,[3] considering aspects such as supportive care, thermoregulation, respiratory protection, fluid replacement, and assessment of fluid balance. [8]
3. Nutritional support, pain management, venous thromboembolism prophylaxis, and infection monitoring (initiate empirical antibiotic therapy if infection is suspected before taking cultures).[3]
4. Medical treatment, including systemic immunomodulatory treatment, skin treatment, mucous membrane treatment (ocular, oral, genital), avoidance of high-risk drugs, and monitoring and treatment of acute complications.[3,4,9]
5. Considerations before discharge: information on the diagnosis and the culprit drug, medical treatment recommendations, explanation of possible long-term medical

complications, and emotional support, including referral to a psychiatrist or psychologist and a support group. [3,10]

SKIN TREATMENT

Different approaches exist for the local treatment of the affected skin without solid evidence on which is superior. However, a conservative approach, leaving detached epidermis in place to act as a biological dressing for the underlying dermis, is preferred. The exposed dermis exudes serum and is covered with necrotic debris, acting as a substrate for microbial colonization. Conservative management involves aspiration or extraction of fluid from prominent blisters and allowing the blister roof to settle on the underlying dermis. Frequent application of a mild emollient to the entire skin is helpful during the acute phase to support barrier function, reduce transcutaneous water loss, and encourage reepithelialization. The use of suitable dressings on exposed dermis reduces fluid and protein loss, limits microbial colonization, and helps control pain. Covering bare skin can also accelerate reepithelialization.[4,6]

In our healthcare facility, a surgical approach was taken with debridement of infected areas that did not respond to conservative management. This involved debridement in the operating room of the lower one-third of the face and anterior chest region.

In conclusion, the management of Toxic Epidermal Necrolysis requires a coordinated and multidisciplinary approach involving specialists from various fields. The key components include early recognition, withdrawal of the culprit drug, supportive care, systemic immunomodulatory treatment, and appropriate local skin management. The conservative approach, leaving detached epidermis in place, is generally preferred, but in certain cases, surgical debridement may be necessary. Regular monitoring, both for complications and psychological support, is crucial for successful management and patient outcomes.[4,6,8]

IMMUNOMODULATORY TREATMENT

Systemic therapies for Toxic Epidermal Necrolysis (TEN) remain controversial. The use of corticosteroids has been associated with increased infections, length of hospital stay, and mortality. However, a multicenter retrospective study combining patients with NET and SJS showed possible benefits with pulse corticosteroids.[4,2] Some centers have investigated cyclosporine[15]. Intravenous immunoglobulin (IVIG) has been widely researched as complementary therapy for TEN. IVIG blocks the in vitro interaction of the Fas receptor with the Fas ligand, preventing keratinocyte death, and has been reported to reduce mortality in NET patients. Although there is not enough evidence regarding immunomodulatory therapy, in our unit, we have Immunoglobulin, so it was decided to initiate it at a calculated dose of 1 mg/kg for 3 days. At 48 hours, a favorable evolution was observed, characterized by a decrease in the progression and necrotic area.[15]

DIFFERENTIAL DIAGNOSIS

Several diseases can be considered in the differential diagnosis, including toxic blistering dermatoses (generalized bullous fixed drug eruption, linear IgA dermatosis induced by drugs), other serious drug reactions (acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms), autoimmune blistering diseases (idiopathic linear IgA dermatosis, pemphigus vulgaris, paraneoplastic pemphigus), major erythema multiforme, and staphylococcal scalded skin syndrome.[5,16.]

PROGNOSIS

The progression lasts about 4 to 5 days after admission, followed by a plateau phase corresponding to progressive reepithelialization. Complete healing can take from a few days to several weeks[3] . The severity and prognosis of the disease can be further outlined using the SCORTEN criteria. SCORTEN is a measure of the severity of toxic epidermal necrolysis, with a higher score indicating a higher patient mortality rate. Seven risk factors are considered: age >40 years, malignancy, total body surface area affected >10%, heart rate >120 beats per minute, blood urea nitrogen >28 mg/dl, serum glucose >250 mg/dl, and serum bicarbonate <20 mEq/L. The absence of a risk factor is scored as zero, and the presence of a risk factor is scored as one. The SCORTEN score ranges from zero to seven, and a higher score corresponds to a higher percentage of patient mortality. In your patient's case, a SCORTEN score of 1 point indicated a mortality of up to 3%, contributing to the favorable prognosis.[1,24,8,10,14]

FOLLOW-UP AND COMPLICATIONS

Long-term outpatient follow-up is important for survivors of NET to manage late complications and identify patients at risk of post-discharge mortality.[8] Dermatological sequelae often include hyperpigmentation, hypopigmentation, hypertrophic scars, and nail dystrophies. Ocular complications occur in 65-89% of cases, including dry eye syndrome, trichiasis, photophobia, symblepharon, corneal inflammation, and neovascularization.[3] Oral and dental complications may include gingival synechiae, gingival recession, dental abnormalities, xerostomia, and increased salivary acidity. Long-term follow-up can also identify chronic pulmonary diseases, renal issues, gastrointestinal complications, etc.[3]

CONCLUSIONS

Toxic Epidermal Necrolysis is a rare entity, and early diagnosis, recognition, and withdrawal of the causative drug, coupled with a multidisciplinary approach, are crucial pillars for treating patients affected by this rare disease. Timely detection of complications significantly influences the patient's prognosis. As there is no consensus or sufficient clinical evidence on the standard management of this disease, each patient must be individualized, and decisions should be

based on close monitoring to promptly detect clinical and paraclinical changes in the natural course of the disease.

REFERENCES

I. Schneider, JA, Cohen, PR . Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Enfatizizing Supportive Measures. *Adv Ther* **34** , 1235–1244 (2017). https://doi-org.pbidi.unam.mx:2443/10.1007/s12325-017-0530-y

II. P. Wolkenstein, YT Wilson, Toxic epidermal necrolysis: the past, the guidelines and challenges for the future *Journal of Dermatology* , volumen 174, número 6, 1 de junio de 2016, páginas 1171–1173, https://doi.org/ 10.1111/bjd.14682

III. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: An Update. Am J Clin Dermatol. 2015 Dec;16(6):475-93. http://doi:10.1007/s40257-015-0158-0. PMID: 26481651.

IV. Creamer D, Walsh SA, Dziewulski P, Exton LS, et al. UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults 2016. J Plast Reconstr Aesthet Surg. 2016 Jun;69(6):e119-e153. doi: 10.1016/j.bjps.2016.01.034. PMID: 27287213.

V. Ingen-Housz-Oro, S., Duong, TA., Bensaid, B. *et al.* Epidermal necrolysis French national diagnosis and care protocol (PNDS; *protocole national de diagnostic et de soins*). *Orphanet J Rare Dis* **13**, 56 (2018). https://doi.org/10.1186/s13023-018-0793-7

VI. Haur Yueh Lee, Wound management strategies in Stevens-Johnson syndrome/toxic epidermal necrolysis: An unmet need, Journal of the American Academy of Dermatology, Volume 79, Issue 4, 2018,Pages e87-e88,ISSN 0190-9622, https://doi.org/10.1016/j.jaad.2018.05.1258.

VII. Meregildo-Rodríguez ED, Asmat-Rubio MG, Sánchez-Carrillo HC, Chavarri-Troncoso FP. Necrólisis epidérmica tóxica secundaria a la administración concomitante de lamotrigina, ácido valproico y fenobarbital. Dermatol Rev Mex 2022; 66 (1): 108-116. https://doi.org/10.24245/dermatolrevmex.v66i1.7439

VIII. Frederick W. Endorf, MD, Leopoldo C. Cancio, MD, Nicole S. Gibran, MD, Toxic Epidermal Necrolysis Clinical Guidelines, , *Journal of Burn Care & Research* , volumen 29, número 5, septiembre-octubre de 2008, páginas 706–712. https://doi.org/10.1097/BCR.0b013e3181848bb1

IX. YK Heng, HY Lee, J.-C. Roujeau Epidermal necrolysis: 60 years of errors and advances, *British Journal of Dermatology* , volumen 173, número 5, 1 de noviembre de 2015, páginas 1250–1254, https://doi.org/10.1111/bjd.13989

X. : Diagnóstico y Tratamiento de la Estomatitis Aftosa recurrente México: Instituto Mexicano del Seguro Social 2011, Fecha de acceso 26.03.23 en: http://www.imss.gob.mx/profesionales/guiasclinicas/Pages/guias.aspx

XI. C.A. Barrera-Ochoa, Use of Intravenous Immunoglobulins and Systemic Corticosteroids in Patients With Toxic Epidermal Necrolysis: Experience of a Hospital in Mexico City, Actas Dermosifiliogr. 2022;113:T294-T29910.1016/j.ad.2022.02.021

XII. Martínez-Cabriales SA, Gómez-Flores M, Ocampo-Candiani J. Actualidades en farmacodermias severas: síndrome de Stevens-Johnson (SSJ) y necrólisis epidérmica tóxica (NET) [News in severe clinical adverse drug reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)]. Gac Med Mex. 2015 Nov-Dec;151(6):777-87. Spanish. PMID: 26581536.

XIII. Oakley AM, Krishnamurthy K. Stevens-Johnson Syndrome. 2023 Apr 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29083827.

XIV. Hasegawa A, Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. F1000Res. 2020 Jun 16;9:F1000 Faculty Rev-612. PMID: 32595945; PMCID: PMC7308994. doi: 10.12688/f1000research.24748.1.

XV. Hasegawa A, Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. F1000Res. 2020 Jun 16;9:F1000 Faculty Rev-612. doi: 10.12688/f1000research.24748.1. PMID: 32595945; PMCID: PMC7308994. doi:10.1186/1750-1172-5-39

XVI. Aihara M, Kano Y, Fujita H et al. Efficacy of additional i.v. immunoglobulin to steroid therapy in Stevens-Johnson síndrome and toxic epidermal necrolysis. J Dermatol 2015; 42:768–77. https://doi.org/10.1111/1346-8138.12925

XVII. Salazar MJ, Valverde JA, Agüero SAC. Síndrome de Stevens-Johnson y Necrólisis Epidérmica Tóxica, un reto diagnóstico y terapéutico . Revista Médica Sinergia. 2020;5(01):308. https://www.medigraphic.com/cgibin/new/resumen.cgi?IDARTICULO=90638