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**Stevens-Johnson syndrome, with ocular  
complications and unfavourable outcome**

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Pharmacy, Sibiu, Romania.***Abstract**

Stevens-Johnson syndrome (SJS) is an acute, rare but serious vasculitis, triggered by a type III hypersensitivity reaction, clinically manifested by a maculo-vesiculo-bullous erythematous eruption and hemorrhagic skin-mucosal erosions, accompanied by rapidly progressive complications. SJS is an important cause of ocular morbidity. The ocular manifestations in SJS are multiple, variable, some very serious, affecting the eyelids, conjunctiva, cornea (infiltrate, corneal ulcerations, with or without corneal perforation), possibly accompanied by ocular complications and sequelae (cicatricial eyelid lesions, corneal perforation, endophthalmitis, corneal leukoma, corneal neovascularization, vision loss). We present the case of a female patient with SJS with ocular manifestations, with acute onset, after drug administration (algotalmin), with serious ocular evolution, with complications and sequelae, with: vascularized corneal leukoma, post-perforated corneal ulcer, symblepharon, Sika keratoconjunctivitis, with decreasing vision in one eye and loss of vision in the other eye. SJS management depends on the clinical aspect and the evolution of the disease, including medical treatment: NSAIDs, corticosteroids, cyclosporine, etanercept, treatment of dry eye syndrome, surgical treatment. A serious disease with an unpredictable evolution, SJS must be monitored in a sustained interdisciplinary manner, with continuous clinical follow-up of the disease and the patient, because SJS poses great problems of morbidity and even mortality, the prognosis through complications and sequelae being reserved.

**Keywords:** SJS, TENS, corneal neovascularization, corneal ulcer, corneal leukoma.

**Introduction**

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis syndrome (TENS) are rare, serious toxidermas with extensive skin-mucosal involvement in the acute phase, followed by complications and sequelae depending on the heterogeneity, severity and extent of the initial lesions.

SJS and TENS are potentially fatal skin-mucosal diseases by affecting organs and systems.

SJS (the limited form of TENS) and LYELL syndrome are variants of TENS, bullous dermatosis of drug-allergic etiology, a serious condition with high morbidity and mortality, characterized by the destruction of the superficial layers of the skin-epidermis and mucous membranes-epithelium, with rapid evolution with complications and the sequels. (14)

TENS is a dermatological emergency because it has a vital prognosis in 1/3 of cases.

Steven-Johnson Syndrome and Toxic Epidermal Necrolysis Syndrome are triggered under similar conditions and are characterized by keratocyte apoptosis, with intraepidermal cell death, secondary to diffuse, cell-mediated vesicular-bullous eruption (3). The difference between them depends on the

extent of the skin lesions: in SJS, skin lesions affect 10% of the skin surface, (TENS) 30%.

In children, the triggering factor of SJS is generally the viral infection: flu, mumps, HSV, coxsackie-virus, Epstein Bars.

In adults, SJS is triggered by (2): adverse drug reaction: Allopurinol, Antiepileptics (carbamazepine, lemotrigen, phenytoin), Antivirotics (nevirapine), Antibiotics (antibacterial sulfonamides - trimethoprim / sulfamethoxazole, fluoroquinolone, tetracycline), NSAIDs, Analgesics (acetaminophen, ibuprofen, naproxen), Antidepressants, Antihistamines, Diuretics (furosemide, acetazolamide); Viral infections: HSV, HZV, HIV, coxsackie, influenza. Bacterial infections: mycoplasma pneumonia, TB, beta-hemolytic streptococcus. Immune system damage: HIV / AIDS, autoimmune diseases - SLE, Behcet, Crohn. Chemotherapy, Organ transplantation, Immunosuppressants (thalidomide), family history, specific genes: HLA-B1502 in Chinese.

### Clinical manifestations in SJS

Stevens-Johnson syndrome is a rare but serious disorder that affects the skin and mucous membrane covering the digestive system, genital tract and eyeballs.

SJS is an acute vasculitis triggered by a type III hypersensitivity reaction (1) that affects the skin and mucous membranes and is characterized by maculo-vesiculo-bullous erythematous rash and hemorrhagic erosions of the mucous membranes with epidermal cell apoptosis and varying degrees of cutaneous mucosal exfoliation. (1,2).

SJS and TENS have an incidence of 1-9 / 1 million people per year, with 5% mortality, more frequently in the elderly, HIV patients.

The onset of SJS is characterized by minimal symptoms (flu like): fever, fatigue, eye pain, burning sensation in the throat, headache, joint pain, cough, rhinorrhea, with onset 1-3 days before the development of cutaneous-mucous rash, without pruritus, with polymorphic lesions.

Over time, the rash appears, red / purple, painful, scattered, which spreads in a few hours / days; parallel to the rash, the mucous membranes (mouth, nose, eyes, genitals) are affected, with the occurrence of blisters and ulcers.

Complications of SJS are rapidly progressive with organ damage (ocular, pneumonia, myocarditis, nephritis, hepatitis, esophageal strictures) and in severe cases, even septic shock.

SJS is a potentially fatal disease with multiple complications that requires a complex therapeutic protocol adapted to the clinical case, indicated with professionalism

and responsibility. (15)

In SJS, there are ENT, respiratory, gastrointestinal, metabolic, pulmonary, renal, hematological, gynecological, genitourinary, nutritional, psychiatric complications and sequelae but also social implications.

SJS is an important cause of ocular morbidity with ocular damage in the proportion of 72-90%.

Ocular complications in SJS, present in 49-81% of cases can be multiple, severe and rapidly progressive (6): dry eyes 59%, corneal inflammation, uveitis, disorders of visual sensitivity to light, keratinization of the free edge of the eyelids, opacification of the cornea, severe irreversible complications accompanied by decrease/loss of visual acuity.

Variable and sometimes severe ocular manifestations up to the point of loss of visual acuity (4) may be:

- Minimal: damage to the skin of the eyelids with scaling and palpebral edema, hyperemia and / or conjunctival chemosis, superficial punctate keratitis
- Moderate: conjunctivitis, infiltrate and / or corneal ulceration
- Severe: palpebral malposition, symblepharon, erosion, ulceration, corneal perforation, endophthalmitis, permanent loss of vision
- Definitive ocular sequelae: scarring entropion, trichiasis, corneal leukoma, corneal neovascularisation, keratinisation of the tarsal and bulbar palpebral margin (4).

Ocular sequelae: photophobia, lacrimation (elements of professional disability), eyelid malpositions (ectropion, entropion, trichiasis, symblepharon requiring eyelid surgery with plasty, excision of pathological mucosa and oral mucosa graft), corneal sequelae with/without corneal neovascularization, corneal leukoma, dry eye syndrome 60%. There is no preventive treatment for sequelae (local corticotherapy is debatable), and curative treatment offers minimal clinical therapeutic correction. (7.19)

### Case presentation of SJS, with unfavourable evolution, with ocular complications and sequelae, although it was properly monitored

Case presentation - Ichim Mihaela, with the diagnosis (at the first hospitalization): drug-induced Lyell syndrome (algalcalmin), pancreatitis, pancytopenia in an infectious context, Anemic Syndrome, Hepatic cytolysis syndrome, AO, blepharoconjunctivitis, OS, keratoconjunctivitis.

The patient is urgently admitted to the Infectious Diseases Service for the appearance of a maculopapular rash

with vesiculobullous lesions, facial edema, fever, altered general condition. These symptoms occurred after self-administration of 2 Algotamin tablets in two different days for back pain. She also received 2 ampoules of algotamin IV. At admission - altered general condition, edema of the face, ulcers covered with abundant secretions, hematous crusts at the level of the oral and genital mucosa, and abundant conjunctival secretions with inability to open the eyes, generalized maculopapular and vesicular rash with serous citrine fluid in tension with a positive Nicolsky sign, with significant skin flaking after spontaneous bursting of bubbles. Impossibility of being fed.

In the Infectious Diseases Clinic, blood tests are performed and antithermics, antibiotics, cortisone, antihistamines treatment is initiated with unfavourable evolution. The patient is referred to the Dermatology Department. In the Dermatology Department: hydroelectrolytic rebalancing is performed, the antibiotic therapy is replaced, the dose of cortisone is increased to 500mg Solumedrol / day, antifungal, gastric protection and disinfectant solutions of the oral, genital, skin cavity are introduced. Under treatment, the evolution is unfavourable and a transfer to the Intensive Care Unit is requested.

In evolution, the skin exfoliation was reduced on 80% of the skin surface, with bleeding ulcerations of the mucous membranes covered with bloody crusts, abundant conjunctival secretions with germ isolation. In evolution, it showed a marked increase in amylase at 1200U / l with a slow progressive decrease, a hepatic cytolysis syndrome that remitted in 10 days, a slight increase in blood glucose. The treatment performed in the ICU consisted in hydroelectrolytic rebalancing, broad spectrum antibiotic therapy according to the indications of the infectious disease specialist, antifungal, vitamin therapy, corticotherapy: 2 days with 1000mg methylprednisolone / day, 2 days with 500mg and one day with 250mg followed by interruption of corticosteroids, anticoagulants, oxygen therapy.

After 2 weeks, the patient complains of visual

disturbances and an ophthalmological consultation is urgently requested which highlights the cornea fluorescein + OS (negative until then) and the treatment with negation is modified one week later. 3 weeks after onset, the patient is transferred to the Dermato-Veneric Section with subfebrility, good general condition, almost complete skin epithelization, with the presence of ulcers on the bilateral mammary areola, more accentuated on the right, ulcers of the oral and genital mucosa. Daily eye examinations did not reveal any pathological aspects.

She is discharged healed with the following recommendations:

- Avoid the administration of ALGOCALMIN
- Diet rich in vitamins
- Local ocular treatment with Nettacin 1 drop x4 / day in the conjunctival sac, Lacrisifi 1x4 / day in the conjunctival sac, kanamycin sulfate ointment x2 / day
- Disinfection of the oral cavity with Stamicin
- Ophthalmological check-up according to the recommendations
- Dermatological check-up directly observed therapy and monitoring

2 months later, the patient is readmitted to the ophthalmology ward, with the diagnosis: SJS, in both eyes: symblepharon, madarosis, trichiasis, Sicca Syndrome (secondary Sjogreen Syndrome), OS corneal abscess, corneal neovascularization. Local treatment is instituted with vitamins, antibiotic ointment, eye lubricants and general treatment: NSAIDs, vitamin therapy.

The patient is readmitted with the diagnosis of keratoconjunctivitis Sicca, trichiasis in both eyes, OS perforated corneal ulcer, vascularized corneal leukoma, visual acuity OD = 0.3cc, visual acuity OS = FPL.

The presented case confirms the positive diagnosis



**Figure 1,2,3** : Patient I.M., 2020. Dg. SJS, AO Keratoconjunctivitis Sicca.OS. Perforated corneal ulcer. Vascularized corneal leukoma. AO. Trichiasis. ODVA=0,3 cc; OSVA=fpl

of SJS with serious evolution, with ocular manifestations with sequelae and complications, with loss of vision in one eye, and highlights the need for an early diagnosis, interdisciplinary collaboration, and treatment of the patient in an appropriate hospital centre. The clinical case, although it was correctly monitored, had an unfavourable evolution.

## Discussions

SJS is a dermatological, ophthalmic medical emergency that requires adequate early diagnosis, hospitalization and directly observed therapy with competent clinical follow-up to limit complications and systemic and ocular sequelae, which can be multiple and severe, with cutaneous-mucosal changes with scars, secondary infections, internal organ damage, and eye damage up to permanent vision loss.(11)

The pathogenesis of the disease is uncertain, currently the disease is considered to be moderately immune with keratocyte apoptosis, followed by cell necrosis (1). The positive diagnosis confirms the pathogenesis of the disease, but it must be rapid and appropriate to the clinical appearance.

SJS is an important cause of ocular morbidity and requires the determination of etiological factors with the correct management of the disease to prevent complications (3,5).

- In the acute vesicular phase (hours / days) conjunctivitis with pseudomembranes can be associated with conjunctival scars with sequelae: ectropion, entropion, trichiasis, lagophthalmia, symblepharon, ankyloblepharone
- Tear film deficiency is present in the late phase, with corneoconjunctival xerosis, which can damage the ocular surface with dry eye syndrome that can cause corneal complications with superficial punctate keratitis, recurrent epithelial defect, decreased visual acuity up to blindness
- Changes in the composition of the tear film can cause corneal, ulcerative complications that can become superinfected
- Uncontrolled infection progresses with complications: corneal perforation, endophthalmitis and panophthalmia with evisceration, enucleation (9)

Ocular complications are present in the acute phase in SJS, in 69-82%, in SNET 50-88%, with dry eye syndrome most frequently - 59%, with ocular sequelae that have a major impact on the daily activity of the patient (3, 9).

In the chronic phase SJS is complicated by multiple scars and sequelae.

Studies of cytokines in tears (9) using the Schirmer test show a significant increase in the acute phase of IL-6, IL-8,

monocytes (MCP) -1 and a decrease in interferon IP-10, IL-6, IL-8 and macrophages (MIP-1 $\beta$ ) in tears during the chronic phase of SJS compared to the concentration in normal tears.

Highlighting these biomarkers would be extremely important for establishing the appropriate treatment in a timely manner to reduce ocular complications and sequelae.

- IL-8 is significantly increased in SJS with neovascularization and / or corneal opacification, and its decrease could reduce the progression to neovascularization
- IL-10 is low in SJS with neovascularization and increased IL-10 levels could suppress the progression of the disease in the chronic phase.

There has been cited in the SJS the genetic predisposition of the disease present in various ethnic groups: HLAB-15-02 shows an association with the induction of SJS through carbamazepine in Chinese; in Japan and Europe, SJS may be associated with HLA31-01 with severe skin reactions; severe complications of the ocular surface in association with HLAA-01-06 were found in the population of Japan and Korea, and HLAB-44-03 in the population of India and Brazil.

There is, therefore, in the SJS, a possible genetic susceptibility with different pathogenesis and phenotypes.

Kim, quoted by Lee (10,11), classifies SJS into the:

- Corneal involvement score with 4 degrees: grade 0 without corneal lesion, grade 1 conjunctival hyperemia, grade 2 the presence of pseudomembranes or corneal epithelial erosion, grade 3 pseudomembranes and corneal erosion
- The presence of systemic lesions is graded between 0-6 by the status of oral or genital erythema, epidermal extension and detachment, liver dysfunction, fever, respiratory disorders, epidermal necrolysis, anemia, increased C-reactive protein, sexual dysfunction, pneumonia

The management of ocular SJS requires the detection of etiological factors and the application of appropriate, early, complex treatment to reduce complications and sequelae.

The clinician must find the best methods with the appropriate therapeutic impact for the disease and the patient, being necessary to individualize the treatment. (3)

## Preventive treatment:

- topical and systemic corticosteroid therapy
- topical and systemic antibiotics
- topical cyclosporine

## Local treatment requires:

- skin handling with caution, serious septic risk
- rehydration, albumin macromolecules
- nutritional intake – 3000-4000 calories
- heating - temperature 300-320
- asepsis - sterile room isolation
- oral, genital antiseptics
- antiseptic eye drops (16)

Local medical treatment limits the extent of complications; in the acute phase, local measures being extremely important (1,12):

- artificial tears
- removal of pseudomembranes
- lysis of the symblepharon ring (glass rod or symblepharon ring)
- topical corticosteroids to prevent scarring
- topical antibiotic to prevent secondary infection
- topical cycloplegic for pain relief, photophobia and reduction of ciliary spasm
- topical cyclosporine
- maintaining the integrity of the corneal epithelium through contact lenses

Systemic medical treatment in SJS includes: glucocorticoids, immunoglobulin, cyclosporine, infliximab, etanercept, plasmapheresis. (8,17)

- systemic corticosteroids that decrease the immune response to exogenous agents, reduce the severity of lesions but may increase the risk of infection

1. methylprednisolone, 4mg/kg/day, 2 days after the fever disappears and the absence of new lesions favours complete re-epithelialization

- intravenous immunoglobulin binds to receptors on the surface of the cornea, prevents apoptosis by reducing complications

2. cumulatively, 02-05g/kg/3 days, favours re-epithelialization and reduces hospitalization

- cyclosporine inhibits calcineurin and decreases cellular activity by preventing apoptosis and promoting faster reepithelialization

3. 3mg/kg/day, or 1mg/kg/day, IV until complete re-epithelialization, then gradually decreasing. (19)

- Etanercept, TNFalpha inhibitor, 25 or 50mg x2/week, until the skin lesions heal; reduces mortality compared to corticosteroids, possible serious side effects, septicemia, respiratory failure
- plasmapheresis can be favourable in 77-100% of cases, after 1 or more maneuvers.

All these drugs, used with discernment, improve the evolution of the disease, lead the reduction of complications, are curatively beneficial, improve the favourable prognosis of the disease.

#### **Surgical treatment:**

- Amniotic membrane transplantation to reduce inflammation and scarring of the ocular surface
- Keratoprothesis
- STEM cell transplant

#### **Management of dry eye syndrome (12):**

- Eye lubricants
  1. Artificial tears
  2. Viscosity increasing agents - carboxymethylcellulose
  3. Antioxidants
  4. Preservatives - benzalkonium chloride
- Biological tear replacements, autologous serum
- Topical cyclosporine 0.05% (restasis)
- NSAIDs: diclofenac, ketorolac, indomethacin
- Biological factors: lubricin (proteoglycan 4)
- Modulation of inflammation: tetracycline
- Macrolides: systemic azithromycin in the treatment of MGD

#### **Surgical treatment:**

1. tarsorrhaphy
2. botulinum toxin
3. amniotic membrane graft

#### **Conclusions**

SJS and TEN represent an acute mucocutaneous syndrome, self-limited, polymorphic, idiopathic or secondary to a drug or after an infectious episode, being triggered by a type III hypersensitivity reaction with erythematous, cutaneous vesicubullous rash and hemorrhagic erosions of mucous membranes.

Ocular manifestations in SJS are progressive, accompanied by sequelae and scars. The most common are conjunctivitis with conjunctival scars, corneal dryness syndrome, inflammation of the iris, ulcerative corneal lesions in severe superinfected cases.

The case presented, although monitored, had a serious evolution of ocular manifestations in the SJS, detected relatively quickly and treated according to medical, dermatological and ophthalmic indications.

The ophthalmic manifestation of the clinical case had a severe evolution, from corneal erosion after vesicular eruption, which was complicated by corneal ulcer and perforation, endophthalmitis and permanent loss of vision. The patient is constantly monitored, and the damaged eye, after 3 years from the onset of the disease, is in normal anatomical and functional conditions. The affected eye within the SJS is an atrophic globe with visual acuity without perception of light projection.

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