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OCULAR COMPLICATION AS A LONG-TERM SEQUELAE OF STEVEN-JOHNSON SYNDROME: WHAT SHOULD WE DO?

Monica Rizky Wigianita[1], Ismi Zuhria[2]
[1 2] Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academic Hospital Surabaya, Indonesia
Corresponding Author email: ismi.zuhria@yahoo.com

Abstract: Ocular surface abnormalities in SJS is a sequelae that has a high chance of progressing, especially in eyes with partial keratinization and conjunctivalization. Even after recovering from skin problems without sequelae, patients can have serious ocular complications leading to blindness despite local and systemic therapy. A 51 years old woman complained that both eyes were red and watery since three years. She also said that her both eyes felt stuck because the eyelashes turned inward for the past 3 years. Initially the patient suffered from SJS (Steven-Johnson Syndrome) in early 2020 with complaints of whole body blisters After the body condition gradually improved after SJS, the patient began to feel changes in the condition of both eyes. The visual acuity of the patient was 5/5 in both eyes. The Schirmer test were 15 mm in right eye and 5 mm in left eye. The Tear Break Up Time (TBUT) examination showed 3 second in right eye and 1 second in left eye. The eyelid had meibomian gland dysfunction for both eyes and the conjunctiva had symblepharon in both eyes. From fluorescein test showed multiple punctate in both eyes. The chronic ocular complications of SJS is characterized by a vicious cycle of ocular surface scarring and inflammation that disturbs the delicate structure and function of the eyelids and tear film and then progresses to further ocular surface damage and swelling. The long-term prognosis of the eye depends on early detection and intensive treatment. To identify the cicatrical abnormalities that cause chronic ocular surface failure, such as limbal cell deficiency and total ocular surface keratinization, the eyelid margin, palpebral conjunctiva, and fornix should be carefully examined.

Keywords: *Steven-Johnson Syndrome, ocular complication, symblepharon, Cicatrical Keratinization, ocular surface reconstruction*

INTRODUCTION

Skin and mucous membranes are affected by the uncommon and severe cutaneous adverse-drug-reaction condition known as Stevens-Johnson Syndrome (SJS). Conjunctiva hyperemia at the acute stage and significant ocular surface keratinization with symblepharon at the end stage are said to describe the variety of ocular involvement in SJS/TEN patients. Ocular surface abnormalities in SJS is a sequelae that has a high chance of progressing, especially in eyes with partial keratinization and conjunctivalization. (Aziza et al., 2022)

Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and SJS-TEN overlap are all severe immunologic dermatobullous disorders that affect the skin and mucous membranes and are typically brought on by medications or infections. SJS is the less severe kind, affecting less than 10% of the body's surface area. The most severe variety, known as TEN, involves more than 30% of the body's surface area. The SJS-TEN overlap, where involvement ranges from 10% to 30%, is categorized as intermediate. Due to their high rates of mortality and morbidity, and the fact that ocular involvement is frequently the most severe long-term sequela, these illnesses, albeit uncommon, are exceedingly important. (Jongkhajornpong et al., 2017)

A 51 years old woman complained of redness and watery on her both eyes since 3 years ago. This patient regularly came to outpatient clinic with the same complaint. She also said that her both eyes felt stuck because the eyelashes turned inward for the past 3 years. Initially the patient suffered from SJS (Steven-Johnson Syndrome) in early 2020 with complaints of whole body blisters. Both eyes at that time were swollen, red, blistered, and blurry. The patient also complained of blistered lips and porous nails. After the body condition gradually improved after SJS, the patient began to feel changes in the condition of both eyes. Both eyes were often

red and watery and felt blocked. The patient has been treated for eyelash removal since 3 years, but was postponed due to the pandemic era for 2 years.

She had suffered Stevens-Johnson Syndrome (SJS) in 2020 and went medication in Gresik Hospital. She didn't have any hypertension nor diabetes mellitus. Patient felt discomfort on her both eyes following her condition after SJS. Patient had been treated by medication of her eyes such as epilation regularly, Cenfresh eye drop every 1h RLE, Hyalub eye drop every 4h RLE, Levofloxacin eye drop every 6h RLE, and Chloramphenicol eye ointment every 8h RLE. Patient also had allergy from paracetamol and amoxicillin. There was no history of trauma nor eye surgery.

From the examination in this patient had visual acuity 5/5 in the right eye and 5/6 in the left eye. Intra oculi pressure within normal limit which was 14 mmHg on her both eyes. Eye movement within normal limit without any pain in both eyes. Anterior segment showed distichiasis and meibomian gland disfunction on her both eyelid. Conjunctiva was hyperemia with symblepharon on 3 and 6 o'clock on her right eye and on 6 and 9 o'clock on her left eye (Fig. 1A). Fluorescent test was positive on her both eyes with multiple punctata (Fig. 1B). Posterior segment examination on both eyes showed round optic disc, defined margin with normal color and normal cup-disk ratio (Fig.2).

From the laboratory testing was within normal limit in blood count (Table1). There was no increasing or decreasing in Free T4 (FT4) with a value 0,80 ng/dL nor in Thyroid-stimulating Hormone (TSH) with a value 2,124 µUI/mL. The corticol serum which taken in the morning showed normal limit (17,4 ug/dL).

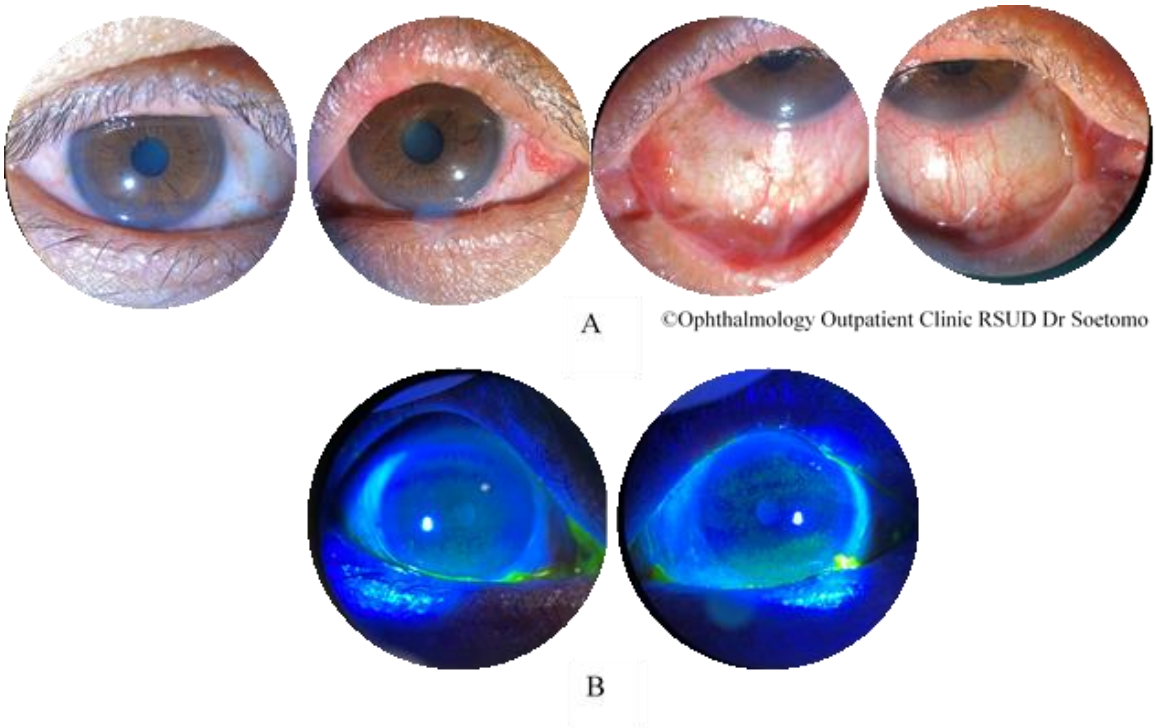

Figure 1. Anterior segment from both eyes.
A. Conjunctiva was hyperemia with symblepharon on her both eyes.
B. Fluorescent test was positive on both eyes with multiple punctata.

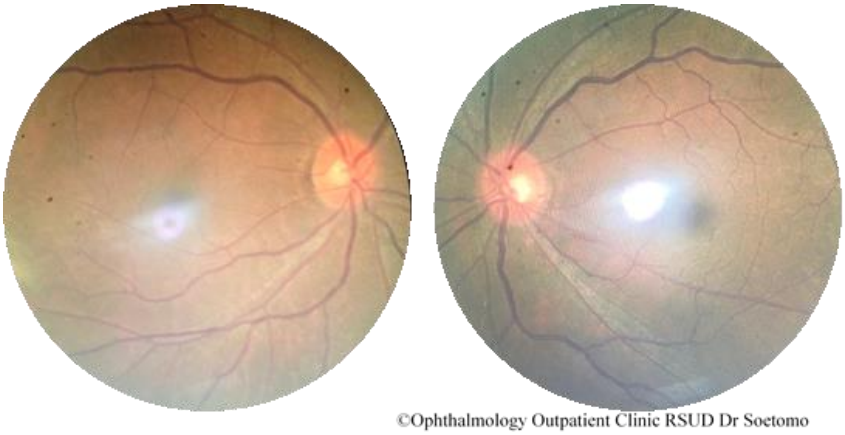

Figure 2. Posterior segment showed within normal limit

From figure 3 showed that patient's nail changed due to SJS. Laboratory test showed within normal limit (Table 1). This patient was diagnosed with RLE Distichiasis, RLE Dry eye Disease, RLE Meibomian Gland Disfuntion, RLE Keratitis Punctata, RLE Symblepharon, and with history of Steven-Jhonson Syndrome. This patient was treated with epilation for both eyes, Cenfresh eye drop minidose every 1 h RLE, Hyalub eye drop minidose every 4 h RLE, Chloramphenicol eye ointment every 8 h RLE, Doxycycline 2 x 100mg po, Vitamin C 1 x 500 mg po, Omega 3 1 x 1 tab po, and was planned to cryotherapy with general anesthesia.

Table 1. Laboratory Blood Test

Parameters	12/06/23	Reference Value
Hb	12,7	11,0 – 14,7 g/dL
Hct	40	35.2- 46.7%
Wbc	6,37	3,37–10(x103 /µL)
Plt	348	150–450(x103 /µL)
Random Blood Glucose	101	<200 mg / dL
BUN	4,0	10-20 mg / dL
Creatinine Serum	0.6	0,5-1,2 mg/dL
SGOT	30	0-37 U/L
SGPT	22	0-55 U/L
Natrium	135	135-145 mmol/l
Kalium	4,10	3,5-5,0 mmol/l
Chloride	100	98-107 mmol/l

METHOD

This study reports a case of ocular complications as long-term sequelae of Stevens-Johnson Syndrome (SJS) in a 51-year-old woman who presented with persistent redness, watering, and inward-turning eyelashes in both eyes over the past three years. These symptoms emerged after the patient recovered from the initial systemic condition of SJS, which had caused widespread body blisters. Despite normal visual acuity (5/5 in the right eye and 5/6 in

the left), the patient experienced chronic ocular complications such as meibomian gland dysfunction, distichiasis, conjunctival hyperemia, and symblepharon, leading to impaired ocular surface health.

The patient underwent a series of diagnostic tests, including the Schirmer test, which indicated low tear production (15 mm in the right eye, 5 mm in the left), and a shortened Tear Break-Up Time (TBUT), suggesting unstable tear film. Fluorescein staining revealed multiple punctate lesions on both eyes, further confirming the presence of ocular surface damage. Posterior segment examination showed normal optic discs, indicating no optic neuropathy. Laboratory tests for thyroid function and cortisol levels were within normal limits.

In terms of treatment, the patient was prescribed eye drops, including Cenfresh, Hyalub, and Levofloxacin, along with regular epilation of eyelashes to manage distichiasis. She had been receiving this regimen for the past three years, but the pandemic had delayed her treatment. The aim of the treatment was to manage the ocular surface inflammation, prevent further scarring, and alleviate symptoms caused by meibomian gland dysfunction and eyelash inversion.

This case highlights the importance of early detection and intensive management to prevent the progression of ocular complications in SJS patients. Careful and regular monitoring of the eyelid margin, palpebral conjunctiva, and ocular surface is essential for detecting and addressing cicatricial abnormalities such as limbal cell deficiency and keratinization, which can significantly affect long-term prognosis and vision.

RESULT & DISCUSSION

The annual incidence of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), an immune-mediated disease that can possibly be fatal and damage vision, is believed to range from 1 to 5 per 1,000,000 people worldwide. The incidence varies between nations. According to a Korean study, between 2010 and 2013, there were 3.96 to 5.03 cases of SJS and 0.94 to 1.45 cases of TEN per million people. The UK reported an incidence rate of 5.76 SJS/TEN cases per million person-years.(Ma et al., 2021)

For SJS, the reported incidence ranges from 1.2 to 6 per million patient-years, while for TEN, it ranges from 0.4 to 1.2. The incidence increases dramatically in the presence of HIV infection and increases with age. Children's mortality rates have been estimated at 7.5%, with SJS mortality rates ranging from 1% to 5% and TEN mortality rates between 25% and 35%.(Jain et al., 2016)

The severity of SJS/TEN is measured using the score of toxic epidermal necrolysis (SCORTEN) grading system. Age, malignancy, tachycardia, first BSA of epidermal detachment, serum urea, serum glucose, and bicarbonate are only a few of the clinical indicators that have been utilized to assess patients. Age, pre-existing comorbidities, hematological malignancy, septicemia, pneumonia, TB, and renal failure are further SJS/TEN mortality predictors. Drug reactions are the most frequent cause of SJS/TEN among the different etiological factors; these include allopurinol, antibiotics, antipsychotics, nonsteroidal anti-inflammatory medicines (NSAIDs), and antiepileptic drugs. Up to 15% of patients may have additional causes, such as mycoplasma infection, herpes simplex virus infection, or other unknown etiologies.(Panpruk et al., 2021)

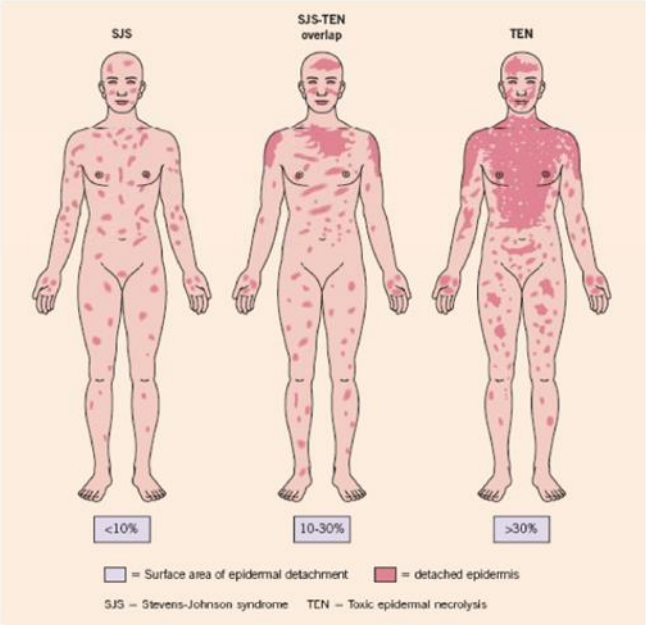

Figure 3. Representation of SJS, SJS-TEN Overlap, and TEN[6]

In figure 3 showed that SJS is the less severe kind, affecting less than 10% of the body's surface area. The most severe variety, known as TEN, involves more than 30% of the body's surface area. The SJS-TEN overlap, where involvement ranges from 10% to 30%, is categorized as intermediate.(Harr & French, 2010)

SJS/TEN is currently thought to be a T cell-mediated hypersensitivity reaction that is delayed. Uncertainty surrounds the pathogenic processes underlying SJS/TEN. The main immunologic component is composed of cytotoxic T lymphocytes (CD8 + T cells) and natural killer (NK) cell immune-mediated responses. The extensive keratinocyte apoptosis and/or necroptosis that results from this immune-mediated cytotoxic reaction against keratinocytes leads to an acute inflammatory vesiculobullous reaction of the skin. Inflammatory cytokines have a significant role in the pathophysiology of acute ocular inflammation in the eye due to basal keratinocytes' early vacuolation and the absence of a lymphocytic infiltrate(Panpruk et al., 2021).

During the start of SJS/TEN, a significant cytokine storm develops on the ocular surface. Patients with SJS/TEN have elevated levels of a number of biomarkers, including IL-6, IL-8, IL-15, IL-10, IL-13, IL-17, TNF-, IFN-, and granulysin (GYLN), in their skin lesions, peripheral blood mononuclear cells, and plasma. Some of them, including GYLN and IL-15, can indicate how severe SJS/TEN is, although research on their connections to ocular involvement is limited.(Panpruk et al., 2021)

Although the pathobiological processes underlying the start of the SJS/TEN complex have been demonstrated to have both an immunological and genetic foundation, they have not yet been fully elucidated.(Jain et al., 2016)

Cellular and molecular immunological mechanism

There is evidence linking a dysregulated innate immune response to SJS with problems on the ocular surface. Ueta and Kinoshita made the hypothesis that the start of SJS with severe ocular surface problems is closely correlated with anomalies in the innate immune system based on their research on allergic reactions that are controlled by ocular surface epithelial cells. Chung et al. suggest a method involving cytotoxic T lymphocytes and natural killer cell-mediated cytotoxicity and propose a role for secretory granulysins as a critical molecule during disseminated keratinocyte death in SJS-TEN. (Jain et al., 2016)

Genetic Association

In certain Asian and European ethnicities, particular alleles at the HLA-A and HLA-B loci raise the risk of drug-induced SJS/TEN. Several single nucleotide polymorphism (SNP) association investigations have employed potential genes linked to innate immunity, allergic responses, or apoptosis in addition to HLA linkage. Toll-like receptor 3 (TLR3) SNPs demonstrated a significant correlation in one research involving Japanese participants, indicating that variants in the TLR3 gene are connected to SJS with ocular surface problems in that community.TLR3's ligand, polyI:C, was discovered to generate a variety of chemicals, including pro-inflammatory cytokines and antiviral and allergy-related compounds, in 214 Human ocular-surface epithelial cells. Additionally, SJS with problems on the ocular surface was highly correlated with the IL4R SNP rs.1801275 (Gln551Arg) and the IL13 rs.20541 (Arg110Gln)212. (Jain et al., 2016)

Ocular manifestations of SJS/TEN can be classified according to the clinical stages: acute and chronic. Initial eye involvement is highly variable and can range from self-limited conjunctival hyperemia to extensive sloughing of the entire ocular surface epithelium, including the tarsal conjunctiva and eyelid margin, leading to symblepharon formation, foreshortening of the fornix, and corneal ulceration or perforation. Late ocular features include cicatricial changes of the conjunctiva and eyelids, severe dry eye, and ocular surface failure.(Jongkhajornpong et al., 2017)·(Lekhanont et al., 2019)

The first two weeks following the beginning of symptoms are when SJS/TEN is in its acute stage. Acute SJS patients typically require intense medical treatment and seldom visit an ophthalmologist. At least two mucous membranes on the body must be inflamed for there to be acute SJS/TEN. Conjunctival hyperemia to nearly complete sloughing of the ocular surface, including the tarsal conjunctiva and eyelid margins, are all examples of acute ocular involvement in SJS/TEN. Bilateral conjunctivitis is the most prevalent ocular disease seen at this point and affects 15–75% of individuals. Conjunctival and/or corneal ulcerations occur in another 25% of hospitalized patients. The tarsal and bulbar conjunctiva must be examined with a meticulous lid eversion and fluorescein staining.(Jain et al., 2016)·(Saeed & Chodosh, 2016)

After they have fully recovered from the acute stage and are able to leave the hospital, the majority of patients visit an eye clinic. They frequently complain of red eyes that are becoming worse, which may or may not have been an issue while they were receiving systemic therapy. The systemic illness is in remission during this phase, the skin lesions have mostly healed, but smoldering chronic cicatrizing conjunctivitis with trichiasis and/or uneven eyelid margins may still be present. The SJS is currently at the sub-acute stage. (Jain et al., 2016)·(Saeed & Chodosh, 2016)

The chronic ocular sequelae that affect up to 35% of SJS/TEN patients include recurrent inflammation and ulceration of the ocular surface in addition to cicatricial problems of the lids. Inflammation and ulceration of the ocular surface continue and lengthen during the disease's chronic stage. The meibomian glands are specifically targeted by lid margin inflammation, which results in extensive destruction of the glands in addition to distichiasis. Trichiasis and cicatricial entropion are brought on by the palpebral conjunctiva's contracture. These alterations help to prevent subsequent corneal damage brought on by frequent blink-related microtrauma to the corneal epithelium of the damaged ocular surface, in addition to chronic dry eye brought on by the lack of lacrimal gland activities. (Jain et al., 2016)·(Saeed & Chodosh, 2016)

The most frequent long-term cause of vision loss in these patients is the degeneration of corneal limbal stem cells. A dry, keratinized ocular surface that prevents corneal or limbal cell transplantation is a hallmark of the disease's last stage. (Jain et al., 2016)·(Saeed & Chodosh, 2016)

Substantial punctate keratopathy, epithelial defect, loss of the Vogt palisades, conjunctivalization, neovascularization, opacification, and keratinization were among the categorized corneal problems. The conjunctival consequences included symblepharon formation and hyperemia. Trichiasis, meibomian gland involvement, mucocutaneous junction involvement, and punctal injury were some of the consequences affecting the eyelids. From the observed complications, the most common ocular complications were the loss of the palisades of Vogt (82.6%) and meibomian gland involvement (73.9%). Corneal neovascularization, opacification, and symblepharon were observed primarily in the chronic SJS eyes. (Jain et al., 2016),(Saeed & Chodosh, 2016)

The most likely cause of eyesight loss was corneal problems. It was also shown that conjunctivalization, a complication of limbal stem cell deficit, is associated with impaired eyesight. Symblepharon development, forniceal shortening, keratinization, lid malposition (such as entropion), and misdirected eyelashes (trichiasis) were among the problems of cicatricial eyelid and conjunctivitis. In eyes with persistent SJS, a significant risk of lid problems was seen. Even in situations when the right care was given right away, eyes without obvious corneal difficulties had modest cicatricial alterations in the eyelid. The lid margin was frequently impacted. They also showed a strong correlation between the degree of ocular involvement and the final visual result. (Jain et al., 2016),(Saeed & Chodosh, 2016)

An expert ophthalmologist must conduct a thorough ophthalmologic examination at the beginning of symptoms and/or the time of admission in order to provide the optimal therapy since early ocular intervention can reduce chronic illness in survivors of SJS/TEN. Fluorescein dye staining is used during a thorough examination to check the cornea, conjunctiva, including the forniceal and tarsal conjunctiva, with special attention to the development of membranes (this requires eversion of the eyelids), and the eyelids for epithelial denudation and ulceration. (Jain et al., 2016),(Saeed & Chodosh, 2016)

When examining the tarsal conjunctiva and fornix, the eyelids can be everted using a Desmarres retractor and/or cotton-tipped applicator. Evaluation of eyelid posture should also be given attention. Lagophthalmos can result in corneal exposure and the consequences mentioned above, either as a result of intubation/sedation or early cicatricial alterations. (Jain et al., 2016),(Saeed & Chodosh, 2016)

Patients who are not sedated and intubated might need painkillers and sedatives to allow for a thorough examination. These ought to be administered following discussion with the main team. The frequency of follow-up exams should be decided on a case-by-case basis, but in the first week after admission, all patients with SJS/TEN should be evaluated every 24 to 48 hours since signs and symptoms might advance quickly. Depending on the severity of the condition, all corneal abnormalities should be treated in a similar manner since infection and perforation might have dire effects. Reevaluation is required if the patient or management service reports any worsening of their signs and symptoms. (Jain et al., 2016),(Saeed & Chodosh, 2016)

The goal of treatment of SJS/TEN is the recovery of the systemic condition and prevention of cicatrical ocular complications. For acute Acute SJS/TEN is a medical emergency associated with significant risk of morbidity and mortality. The mainstay of ocular therapy in the acute phase was a lubrication with preservative-free artificial tears and ointments. For conjunctival hyperemia without epithelial defects can use topical steroids and antibiotics. For Conjunctival, corneal, or eyelid margin defects with or without membranes the use of amniotic membrane graft with topical steroids and antibiotics may useful (Fig.4). [9]

The aim of chronic management in SJS for rehabilitation of visual function and treatment of secondary dry eye disease and the mechanical abnormalities of the eyelids and eyelashes, which can cause ocular surface trauma and inflammation. Scleral contact lenses may improve patient comfort and vision.[10]

Living donor or cadaveric limbal stem cell transplantation and cultivated oral and nasal mucosal epithelial transplantation have been performed but are less successful in cases of extreme dry eye. Penetrating keratoplasty is associated with an extremely poor prognosis in patients with chronic disease. For chronic SJS treatment can be seen in figure 5.

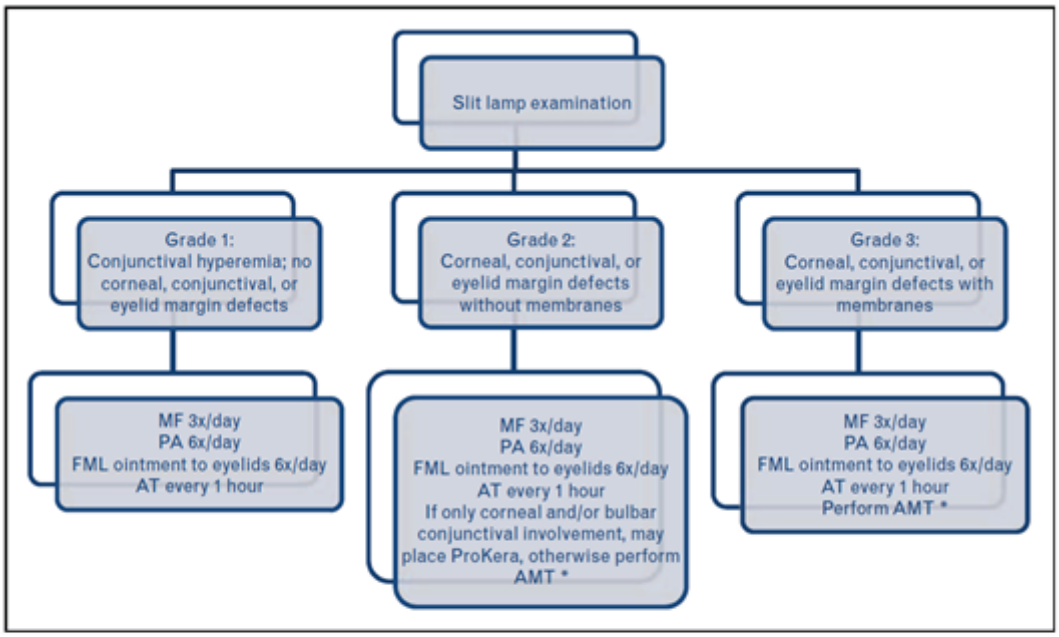

Figure 4. Diagram outlining suggested management of ocular manifestations in acute Stevens–Johnson syndrome and toxic epidermal necrolysis. AMT: amniotic membrane transplantation; AT: artificial tears; FML: fluorometholone 0.1%; MF: moxifloxacin 0.5%; PA: prednisolone acetate 1%.

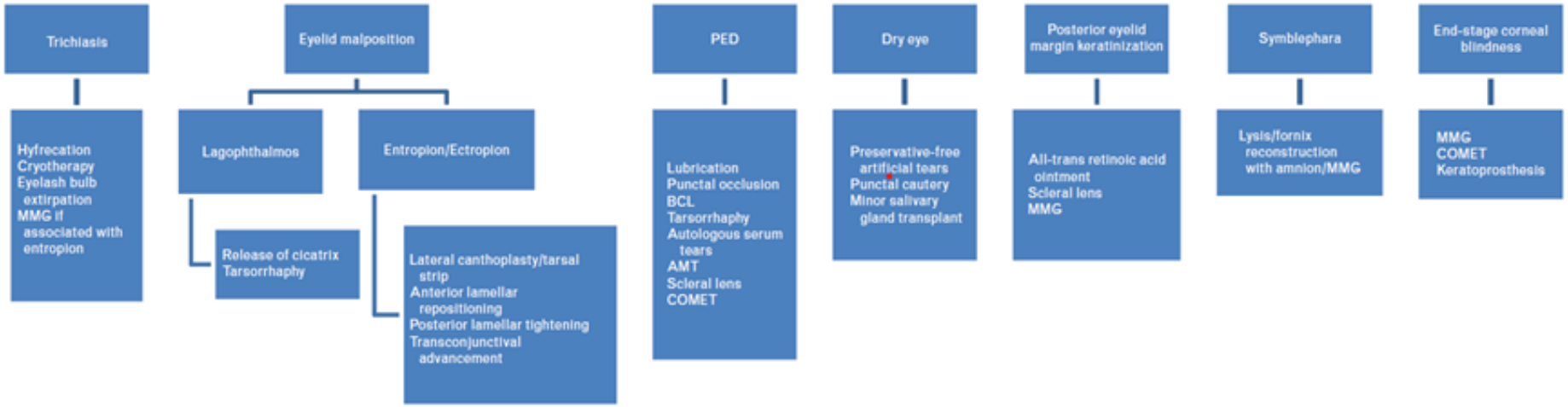

Figure 5. Medical therapeutic approaches to chronic ocular Stevens–Johnson syndrome and toxic epidermal necrolysis.

CONCLUSION

The chronic stage is characterized by persistent ocular surface inflammation, cicatricial sequelae, and a persistently dry surface. Instead of attempting to repair the damage afterwards, it is advised to prevent symblepharon, eyelid malposition, dry eye, and corneal illness. Normal characteristics of the chronic stage of SJS include LSCD, severe dry eye, and abnormalities of the lid border.

In the chronic phases of the illness, systemic immunosuppressive treatment may be beneficial for certain individuals, but overall, the usefulness of topical and systemic medications is limited. Correcting lid margin abnormalities and shielding the ocular surface from lid margin keratinization are the two most crucial steps in lowering chronic ocular surface failure. The ocular surface is stabilized by oral MMG, which also lessens the harm caused by the keratinized lid edge.

REFERENCES

Aziza, Y., Harada, K., Ueta, M., Fukuoka, H., Kinoshita, S., & Sotozono, C. (2022). Challenges in the management of bilateral eyelid closure in Stevens-Johnson Syndrome. *American Journal of Ophthalmology Case Reports*, *26*(February), 101473. https://doi.org/10.1016/j.ajoc.2022.101473

Harr, T., & French, L. E. (2010). Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet Journal of Rare Diseases*, *5*(1), 39. https://doi.org/10.1186/1750-1172-5-39

Jain, R., Sharma, N., Basu, S., Iyer, G., Ueta, M., Sotozono, C., Kannabiran, C., Rathi, V. M., Gupta, N., Kinoshita, S., Gomes, J. A. P., Chodosh, J., & Sangwan, V. S. (2016). Stevens-Johnson syndrome: The role of an ophthalmologist. *Survey of Ophthalmology*, *61*(4), 369–399. https://doi.org/10.1016/j.survophthal.2016.01.004

Jongkhajornpong, P., Lekhanont, K., Siriyotha, S., Kanokrungsee, S., & Chuckpaiwong, V. (2017). Factors Contributing to Long-Term Severe Visual Impairment in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Journal of Ophthalmology*, *2017*. https://doi.org/10.1155/2017/2087578

Lekhanont, K., Jongkhajornpong, P., Sontichai, V., Anothaisintawee, T., & Nijvipakul, S. (2019). Evaluating Dry Eye and Meibomian Gland Dysfunction with Meibography in Patients with Stevens-Johnson Syndrome. *Cornea*, *38*(12), 1489–1494. https://doi.org/10.1097/ICO.0000000000002025

Ma, D. H. K., Tsai, T. Y., Pan, L. Y., Chen, S. Y., Hsiao, C. H., Yeh, L. K., Tan, H. Y., Lu, C. W., Chen, C. B., & Chung, W. H. (2021). Clinical Aspects of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis With Severe Ocular Complications in Taiwan. *Frontiers in Medicine*, *8*(May), 1–9. https://doi.org/10.3389/fmed.2021.661891

Panpruk, R., Puangsricharern, V., Klaewsongkram, J., Rerknimitr, P., Kittipibul, T., Chongpison, Y., & Buranapraditkun, S. (2021). Clinical parameters and biological markers associated with acute severe ocular complications in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Scientific Reports*, *11*(1), 1–10. https://doi.org/10.1038/s41598-021-99370-1

Saeed, H. N., & Chodosh, J. (2016). Ocular manifestations of Stevens-Johnson syndrome and their management. *Current Opinion in Ophthalmology*, *27*(6), 522–529. https://doi.org/10.1097/ICU.0000000000000312