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Vulvovaginal and ocular involvement and treatment in female patients with Stevens–Johnson syndrome and toxic epidermal necrolysis: A review

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ABSTRACT

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious adverse cutaneous drug reactions, characterized by epidermal detachment and mucous membrane involvement. SJS/TEN is more common in female patients, with unique findings in the ocular and vulvar regions. Early recognition and intervention, as well as long-term follow-up, are crucial to prevent devastating scarring and sequelae. This review examines the vulvar and ocular manifestations of SJS/TEN and describes the current treatment recommendations for female patients, requiring close consultation and collaboration among dermatology, ophthalmology, and gynecology.

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What is known about this subject in regard to women and their families?

- Stevens–Johnson's syndrome (SJS) and toxic epidermic necrolysis (TEN) are more common in women.
- Long-term sequelae can profoundly affect vaginal and ocular surface health, including vision loss and dry eye syndrome.

What is new from this article as messages for women and their families?

- Early intervention with a multidisciplinary approach, including dermatology, ophthalmology, and gynecology, is crucial to reduce scarring and improve outcomes and the quality of life of female patients with SJS and TEN.
- Long-term follow-up with dermatology, ophthalmology, and gynecology is also necessary in female survivors of SJS/TEN because of ongoing chronic inflammation and the higher risk for ocular surface disease and gynecologic neoplasias.
- Sex-related differences in ocular surface may predispose women to more severe ocular complications in SJS/TEN, and future studies are needed to investigate the inflammatory response of female survivors with SJS/TEN.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immune-mediated, life-threatening, adverse drug reactions, characterized by epidermal and mucous membrane detachment. The incidence of SJS/TEN ranges from 1.6 to 9.2 cases per million per year in the United States, and the mortality rate can approach 15% to 49%, making early intervention vital (Seminario-Vidal et al., 2020).

Several manuscripts from around the world suggest that SJS/TEN is more common in female than male patients, with an incidence ranging from 52% to 68% (Hsu et al., 2016; Kannenberg et al., 2012; Micheletti et al., 2018; Saka et al., 2013; Sekula et al., 2011; Sunaga et al., 2020). The prevalence of vulvovaginal involvement in women with SJS/TEN is as high as 70%, but may be underestimated because of the focus on critical care in the early phase of the illness or the sensitive nature of examination of the genitourinary area (Kaser et al., 2011; Meneux et al., 1998).

Several retrospective studies on ocular SJS/TEN report that female patients are more commonly affected (Cabañas Weisz et al., 2020; Kohanim et al., 2016b; Power et al., 1995; Saka et al., 2019; Sotozono et al., 2015). The severity of ocular disease in women with SJS/TEN has not been well studied, partly because the results are often presented as one group, but a few reports indicate that women have worse disease. Kim et al. (2015) reported that female sex was the strongest prognostic factor for the severity of chronic ocular-surface complications and worse final vision in survivors with SJS/TEN. Also, in a retrospective study on the ocular sequelae of SJS/TEN, 64% to 67% of patients with severe or very severe ocular disease were female (Sotozono et al., 2015). More recent studies report an association between female sex and worse final vision in patients with chronic ocular complications in SJS/TEN or higher rates of lid-related keratopathy in adult female patients with SJS (Hall et al., 2021; Shanbhag et al., 2020c).

These findings highlight the need for more sex-specific studies in SJS/TEN to investigate whether the known structural differences in the female ocular surface predisposes women to post-SJS/TEN complications, such as dry eye disease, which affects 59% of survivors (Gueudry et al., 2009; Matossian et al., 2019; Nelson et al., 2017). Women have greater expression of the transglutaminase 1 gene, which plays a role in surface keratinization, as well as lower conjunctival goblet cell numbers and more meibombian gland dysfunction, all contributing to the loss of homeostasis of the tear film and dry eye symptoms (Connor et al., 1999; Sullivan et al., 2017; Viso et al., 2012). Other risk factors, such as menopause, hormone replacement therapy, and autoimmune diseases, also play a role (Clayton, 2018; Nelson et al., 2017; Vehof et al., 2020).

The pathogenesis of ocular SJS/TEN disease severity and dry eye in female survivors is likely due to a combination of sex-specific predisposition for ocular-surface inflammation and chronic sequelae, such as keratinization and cicatricial changes (Iyer et al., 2020; Kohanim et al., 2016a; Lekhanont et al., 2019a; Matossian et al., 2019; Singh et al., 2021b; 2021c; Sotozono et al., 2018; Sullivan et al., 2017). Despite the existing knowledge gap concerning the female inflammatory response in SJS/TEN, abatement of the acute phase is known to lead to improved long-term outcomes (Gregory, 2011; Kohanim et al., 2016a; Saeed and Chodosh, 2016; Shanbhag et al., 2020a). This review will focus on the pathophysiologic changes and therapies in vulvovaginal and ocular mucosal surface involvement of SJS/TEN and provide recommendations for the management of SJS/TEN.

Vulvovaginal involvement in SJS/TEN

Women with vulvovaginal SJS/TEN experience significant pain and morbidity and have the potential for long-term complications, especially when not recognized and treated early in the course of disease. This section reviews the gynecologic surface anatomy and the pathophysiology and guidelines for treatment of the vulvovaginal involvement in SJS/TEN.

Gynecologic anatomy

Several anatomic structures make up the external part of the female genitalia, collectively called the vulva. The vulva protects a woman's sexual organs, urethral orifice, and vagina. The skin of the mons pubis, labia, clitoris, and perineum is derived from the embryonic ectoderm and has a keratinized, stratified, squamous structure with sweat glands, sebaceous glands, and hair follicles (Jones, 1983).

Vagina

The vagina is of mesodermal origin and has nonkeratinized squamous epithelium that is responsive to ovarian steroid hormone cycling, which changes with menopause (Nauth, 1993). Lactic acid–producing *Lactobacillus* species predominate in the vaginal flora of healthy women protecting against pathogenic organisms

and inflammatory conditions (Marshall and Tanner, 1981; Van De Wijgert et al., 2014). Therefore, vaginal biome dysbiosis is associated with an increased risk of infection and inflammation (van de Wijgert and Jespers, 2017).

Urethra

The urethra is a tubular structure approximately 3 cm in length and is the distal portion of the urinary tract. The urethra is situated in the vulva, anterior to the vaginal introitus. An epithelial, lamina propria, and muscular layer surrounds the urethral lumen, with adipose and loose fibroconnective tissue separating the urethra from the anterior vagina (Mahoney et al., 2017; Mazloomdoost et al., 2017).

Acute gynecologic involvement in SJS/TEN and management

Acute vulvar SJS/TEN lesions can affect both the keratinized and nonkeratinized epithelia and are typically erosions and ulcerations, with bullae rarely seen. Patients may experience pain, swelling, and dysuria. When the vagina is involved, there is erosive and extensive vaginitis with purulent blood-stained vaginal discharge, although at times there may be no discharge or symptoms and a high index of suspicion is necessary. Without treatment, the time to resolution of the vulvovaginal lesions ranges from 7 to 56 days (Meneux et al., 1998).

Vulvar examination

The importance of a daily total body skin examination, inclusive of the vulvar mucosa, perineum, perianal skin, and anus, cannot be overstated. This examination is noninvasively accomplished by having the patient draw her heels up toward her buttocks and allow the knees to drop to the sides, or the patient may lie on her side, top knee slightly bent and in front of the bottom leg, with the buttocks spread by the examiner. Such examination should be completed daily until discharge because delayed mucosal inflammation is possible, as are side effects from medical management, such as vaginal candidiasis.

Although a speculum examination would reveal the extent and location of vaginal ulceration and desquamation, such an examination is painful and often distressing for the patient. Experts have suggested assuming there is vaginal involvement in such cases, especially when the vaginal introitus is involved (O'Brien et al., 2019).

Management of acute SJS/TEN

To date, there have been no prospective clinical trials to study the treatment and supportive care of women with vulvovaginal SJS/TEN; recommendations rely on expert opinion from dermatologists and gynecologists (Emberger et al., 2006; Meneux et al., 1998; O'Brien et al., 2019). The goals of therapy should be to protect vaginal function by decreasing adhesion formation and agglutination, as well as limiting metaplastic and potentially neoplastic changes in affected tissue. Mainstays of care include the insertion of a Foley catheter, topical application of corticosteroids, menstrual suppression, and vaginal dilator physical therapy, as described in detail in Table 1 and Figure 1 (Kaser et al., 2011; O'Brien et al., 2019).

Subacute vulvovaginal SJS/TEN

Follow-up with gynecology is necessary after hospital discharge to manage subacute vulvovaginal SJS/TEN inflammation and monitor for any evolving side effects from medications. Rates of follow up with gynecology after discharge have not been well studied, but likely are reflective of the low rates of gynecologic consultation in the hospital phase.

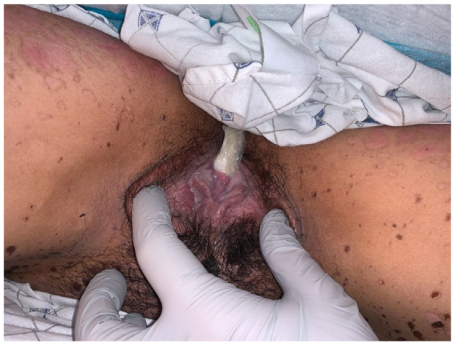

Fig. 1. Photograph of dilation therapy during re-epithelialization, 12 days after admission for toxic epidermal necrolysis. In this case, a vaginal ultrasound endocavity probe cover containing rolled 4×4 gauze pads was used to create a soft, flexible dilator for this virginal woman with a history of tampon use.

Chronic vulvovaginal sequelae of SJS/TEN

Although chronic urogenital compilations are less common than at other mucosal sites, several chronic manifestations are well described, including anatomic alterations, physiologic changes, dysthesia, and psychosocial impairments (Emberger et al., 2006; Wilson and Malinak, 1988).

Scar tissue and stenosis

Mucosal erosions promote adhesions of the vagina or labia, and the resultant scar formation may lead to vaginal synechiae, loss of vulvar tissue architecture (agglutination), fusion of the anatomic structures of the vulva, and stenosis or occlusion of the vagina and urethra (De Jesus et al., 2012; Hart et al., 2002). Possible sequelae from obstructed urinary stream and menstrual egress include urinary retention, recurrent cystitis, postvoid dribbling, hematocolpos, hematometra, and endometriosis (Meneux et al., 1998; Van Batavia et al., 2017).

Metaplasia

Metaplastic cervical or endometrial epithelium in the vaginal wall has been described in multiple case reports after SJS/TEN in adults. This is thought to result from p63 suppression in the basal cells of the vaginal and cervical epithelium in SJS/TEN, which allows for vaginal squamous epithelium to be replaced by glandular epithelium (Noël et al., 2005). Vulvovaginal adenosis has the potential to transform into squamous cell, mucinous, and clear cell carcinoma of the vagina (Ghosh and Cera, 1983; Kranl et al., 1998; Scurry et al., 1991). The risk of vulvovaginal metaplasia and neoplasia in SJS/TEN survivors has not been studied to date (Emberger et al., 2006). SJS/TEN survivors with persistent gynecologic symptoms or lesions should undergo punch biopsy of the vulva and vagina and have close observation with colposcopy if the biopsy is positive for adenosis (Kaser et al., 2011).

Genital symptoms in survivors of SJS/TEN

Sexual dysfunction secondary to SJS/TEN is likely more common than reported in the literature. There are no published studies reporting sexual function in survivors of SJS/TEN, although several case reports and patient focus groups mention dyspareunia, chronic pruritus and pain, and vulvodynia as sequelae (Meneux et al., 1998; Petukhova et al., 2016). Other genital sequelae include functional dryness, tissue fragility, and bleeding (Chang et al., 2020). Early return to sexual intercourse after re-epithelialization (or dilator therapy in patients not sexually active) and referrals to pelvic floor physical therapy can help with vulvodynia, dyspareunia, vaginismus, or involuntary contracture of musculature, as well

Table 1
Medical management of and gynecologic procedures in acute vulvovaginal SJS/TEN

Medical management of acute vulvovaginal SJS/TEN	
General care	• Sitz baths with warm water, gentle irrigation of the vulva with perianal irrigation bottle (O'Brien et al., 2021).
Urethral erosions and/or dysuria	• Foley catheter placement allows for assessment of fluid status and stents the urethra open to prevent adhesions and strictures, aids in pain relief.
Vulvar erosions (Fig. 1)	• Ultrapotent glucocorticoid ointment applied daily for 5-7 days in acute phase; ointments preferred. • Zinc oxide or white petrolatum applied as barrier after corticosteroid.
Vulvar pain	• Viscous lidocaine 2% may be applied.
Intravaginal erosions Speculum examination may be too painful for patient; thus, vaginal involvement can often be assumed when vulvar erosions are present	• After menarche: Moderate-to-ultrapotent corticosteroid ointment applied intravaginally with a vaginal dilator, vaginal suppository, or gloved finger, depending on patient comfort. • In young women without a history of tampon use, the hymen may remain intact, making intravaginal medication use uncomfortable. Providers may inquire if patients have been sexually active or have a history of using tampons to recommend the most comfortable technique for application (O'Brien et al., 2021).
Menstrual suppression	• Hormonal suppression may decrease inflammation of the vagina/vulva and prevent vaginal adenosis and endometriosis. • Mechanisms by which menstrual suppression may help: It is hypothesized that the exposure of vaginal ulcers to menstrual blood may lead to direct implantation of Müllerian-derived columnar cells (Emberger et al., 2006; Noel et al., 2005). Also, glandular proliferation is regulated by estrogen; epithelium in vaginal adenosis stains positive for estrogen receptors, in contrast to native vaginal epithelium.
Gynecologic procedures in acute vulvovaginal SJS/TEN	
Vaginal dilation therapy	• Vaginal dilator therapy may prevent scarring rather than reverse scarring that has already occurred and thus should begin early in course of disease. • Hypoallergenic silicone dilators are often available from radiation oncology departments, or online at electronic commerce stores. Size can be guided by prior sexual activity or tampon use (Kaser et al., 2011; O'Brien et al., 2021). In the event a vaginal dilator is not available, rolled gauze placed into an ultrasound endocavity probe cover can be used instead (Fig. 1). • Twice-daily sessions are recommended where the dilator is inserted, ideally by the patient. The dilator may be lubricated with either corticosteroid ointment or water-based lubricant and then either inserted and left in place for 10-20 minutes or inserted and removed quickly. If the patent is struggling with compliance with the former regimen, the latter regimen may be easier to tolerate and confer similar benefits (O'Brien et al., 2021). • Patient privacy is important during dilator therapy, and allotting therapy time during the day to prevent interruption by family and staff members is paramount. • Depending on the age and ability of the patient, nursing and/or family members may need to be instructed on how to apply medication and insert the dilating device (O'Brien et al., 2021).

SJS, Stevens–Johnson syndrome; TES, toxic epidermal necrolysis.

as improve pelvic floor muscle tone (Kaser et al., 2011; Lee et al., 2016; O'Brien et al., 2019).

Ocular considerations in SJS/TEN

The ocular surface is affected in 46% of 88% of all patients with SJS/TEN. Late ocular complications of SJS/TEN are associated with the severity of ocular disease in the acute phase (Power et al., 1995; Sotozono et al., 2007; 2015; Yoshikawa et al., 2020b). Progression of SJS/TEN ocular-surface inflammation can lead to severe dryness, ulceration, scar tissue formation, and keratinization of the ocular surface, affecting long-term visual outcomes and quality of life in these patients (Gueudry et al., 2009; Power et al., 1995; Tougeron-Brousseau et al., 2009). Therefore, early recognition of ocular involvement and implementation of targeted treatment are essential to downregulate inflammation and prevent sequelae (Gregory, 2011; Kohanim et al., 2016a; Saeed and Chodosh, 2016; Saeed et al., 2020). This is particularly important for female patients because they have a higher risk for dry eye disease and may be more susceptible for chronic ocular-surface disease in SJS/TEN (Matossian et al., 2019; Smith et al., 2007; Sullivan et al., 2017).

Ocular-surface anatomy

Table 2 describes the ocular-surface components in health along with pathophysiologic changes observed in patients with SJS/TEN. The ocular surface consists of the eyelids, meibomian glands (MG), conjunctiva, cornea, main and accessory lacrimal glands (LG), and tear film (TF). All elements of the ocular surface are interconnected and contribute to its health, maintenance, and repair (Biber, 2013; Craig et al., 2017). The eyelids provide protection; house the MGs, which release tear-stabilizing lipid into the TF; and spread the TF over the surface to avoid premature evaporation. With every blink, the TF lubricates the surface and distributes nutrients (Willcox et al., 2017). The human TF proteome also contains 1800 different proteins, including immunoglobulins, cytokines, growth factors (GF), neuropeptides, lysozyme, and matrix-metallopeptidases to protect and maintain the ocular surface (Willcox et al., 2017). The corneal epithelium is continuously supplied by limbal stem cells (LSCs) residing at the corneal margin and depends on GF for repair (Holland et al., 2013). Finally, the conjunctiva, a mucosal surface, is a protective barrier that covers the entire ocular surface (except for the cornea) and is severely affected in SJS/TEN (Harvey et al., 2013).

Ocular-surface changes in SJS/TEN

Ocular-surface homeostasis is disrupted in ocular SJS/TEN, and inflammation ranges from mild conjunctivitis to suppurative membranous conjunctivitis, often followed by fibrosis (Kohanim et al., 2016a). Ocular disease severity is considered the primary risk factor for long-term complications in SJS/TEN, and the goal of ocular therapy is to treat inflammation aggressively and as early as possible to prevent scarring and chronic inflammatory changes (Gregory, 2011; Kohanim et al., 2016a; Thorel et al., 2020).

Table 2
Ocular-surface components in health and SJS/TEN

Components of ocular surface	Function	SJS/TEN-related damage	Previous studies
Eyelids	• Protection • Blink reflex • Distributes tear film	• Decreased blinking • Lid-related keratopathy • Trichiasis with mechanical damage of ocular surface • Keratinization of posterior lid margin in up to 70% of patients, mechanical damage, inflammation.	• Gurumurthy et al., 2018; Shanbhag et al., 2020; Singh et al., 2021a • Iyer et al., 2020
Meibomian gland orifices at lid margin	• Provide lipid layer to tear film	• Meibomian gland dysfunction in 87.5% of patients • Loss of meibomian glands in up to 79% of patients and premature tear film evaporation	• Lekhanont et al., 2019a; Shanbhag et al., 2020; Sotozono et al., 2018; Yoshikawa et al., 2020a
Conjunctiva	• Protective barrier • Loose, allows for motility	• Epithelial defects, fibrinous membranes, scarring, symblepharon formation, loss of fornices, chronic inflammation, chronic neutrophilic infiltrate	• Di Pascuale et al., 2005; Sotozono et al., 2018; Williams et al., 2013; Yoshikawa et al., 2020a
Goblet cells (embedded in conjunctiva)	• Produce mucins for lubrication and tear film component	• Loss of up to 95% of goblet cells, loss of mucin production, increased friction and mechanical damage.	• Nelson and Wright, 1984
Accessory lacrimal glands	• Aqueous tear film contribution	• Destruction from conjunctival scarring resulting in dry eye disease	• Kohanim et al., 2016; Yang et al., 2016
Lymphoid tissue layer in lamina propria: Resident immune cells: T cells (CD3+), macrophages (CD68+), natural killer cells, IgA-producing plasma cells and mast cells Conjunctiva-associated lymphoid tissue is part of mucosa-associated lymphoid tissue, and lymphoid follicles are predominantly in tarsal conjunctiva (Hingorani et al., 1997; Knop and Knop, 2000)	• Protection, immune response	• Acute and chronic inflammation • Granzyme (from natural killer T cells) • IL-1, IL-1α, IFN-γ, IL-8, IL-15, IL17a, monocyte chemoattractant protein-1, macrophage inflammatory protein-1, tumor necrosis factor, basic fibroblast growth factor	• Iyer et al., 2020; Yagi et al., 2011; Yoshikawa et al., 2020b
Innate Immune system	• Protection, immune response	• Profibrotic chronic inflammation • Neutrophils infiltrate the conjunctiva of ocular SJS, even in the absence of clinical inflammation	• Ueta, 2018; Ueta and Kinoshita, 2010; Williams et al., 2013
Cornea	• Avascular, transparent • Focusses images	• Cornea neovascularization, scarring, loss of transparency, epithelial defects, corneal ulceration perforation, microbial keratitis in 34% of patients	• Singh et al., 2021b; Sotozono et al., 2007
Epithelium	• Nonkeratinized squamous • Renews itself every 5-7 days • Highly dependent in growth factors for maintenance	• Epithelial defects, loss of growth factors with inability to heal defects, susceptibility to infection, keratinization	• Kohanim et al., 2016; Vera et al., 2009
Corneal nerve plexus	• Lacrimal functional unit regulates corneal sensitivity, blink reflex, tear production • Production of neurotrophic growth factor to maintain corneal nerves and epithelium (Mastropasqua et al., 2017; Pflugfelder, 2011)	• Loss of corneal nerves, shortening, nerve beading, and tortuosity	• Vera et al., 2009
Limbal stem cells (at the corneal margins)	• Responsible for corneal epithelial regeneration and barrier for neovascularization • Highly dependent on growth factors produced by the lacrimal gland for healthy epithelial growth, integrity, and repair (Klenkler and Sheardown, 2004)	• Limbal stem cell loss, nonhealing epithelium, conjunctival overgrowth • Loss of transparency, loss of vision	• Kohanim et al., 2016; Lopez-Garcia et al., 2011; Sotozono et al., 2007; Vera et al., 2009)

(*continued on next page*)

Table 2 (*continued*)

Components of ocular surface	Function	SJS/TEN-related damage	Previous studies
Tear film	• Provides moisture, nutrients, protection to ocular surface • Contains 1800 different proteins, including lysozyme and growth factors, IgA	• Reduced or severe loss of tear film and growth factors with dry eye disease, pain, photophobia, surface epitheliopathy	• Lekhanont et al., 2019b; Sotozono et al., 2018
Lipid layer	• Produced by meibomian glands	• Loss of meibomian glands with premature tear evaporation	• See meibombian glands
Aqueous layer	• Produced by main and accessory lacrimal glands	• Periductular fibrosis of tear gland, loss of growth factors, loss of accessory lacrimal glands from scarring	• See lacrimal gland
Mucin layer	• Produced by goblet cells in the conjunctiva (gel form) and conjunctival epithelium (soluble form)	• Decreased mucins; increased dryness, friction, and mechanical damage	• Di Pascuale et al., 2005
Lacrimal glands		• Periductular fibrosis of tear gland	• Singh et al., 2021b
Main	• Produces aqueous tear film, lysozyme, growth factors to maintain and protect ocular surface	• Loss of growth factors	
Accessory lacrimal glands	• Embedded in conjunctiva	• See conjunctiva	

IL, interleukin; SJS, Stevens–Johnson syndrome; TES, toxic epidermal necrolysis

Table 3
Grading and treatment guidelines in acute ocular Stevens–Johnson syndrome/toxic epidermal necrolysis (adapted from Gregory, 2016)

Before grading, flush ocular surface with balanced salt solution or 0.9% saline solution to clear mucus. Always evert upper and lower lid to examine the palpebral conjunctiva for inflammation. For fluorescein staining, touch inside of lower lid briefly with fluorescein strip and have patient blink or open and close lids manually (Fig. 2).

Grade	Treatment
Mild	
Conjunctival hyperemia only	Preservative-free artificial tears
No fluorescein staining	Close daily observation
Moderate	
Lid margin fluorescein stain <1/3 of length	Preservative-free artificial tears every hour
Conjunctival hyperemia	Broad-spectrum antibiotic drop (e.g., moxifloxacin) 4 × /day
Conjunctival fluorescein stain <1 cm	Topical prednisolone acetate 1% drops 4 × /day
Corneal punctate staining, but no defects	Consider bedside amnionic membrane disc insertion to reduce inflammation (Fig. 3)
Severe	
Lid margin fluorescein stain >1/3 of length	Same as above + amnionic membrane transplant to cover complete ocular surface, including lid margins
Conjunctival yellow membranes or peelable pseudo membranes	
Conjunctival fluorescein stain >1 cm	
Corneal epithelial defect any size	
Very severe	
Same as severe +	Same as above + may need repeat amnionic membrane transplant within 1-2 weeks
>1/3 of lid margin and >1 eye lid affected	
Conjunctival fluorescein stain multiple areas	
Corneal epithelial defects any size	

Acute ocular involvement and management in SJS/TEN

The first sign of acute ocular involvement within 1 to 5 days is conjunctival hyperemia. Once conjunctivitis occurs, medical management should be initiated, and the ocular surface should be examined daily for epithelial defects, which can be visualized with nontoxic fluorescein stain for grading and can be performed at bedside (Table 3; Fig. 2). Persistence of epithelial defects poses a risk for infection and scarring (Gregory, 2016). Treatment is advanced based on disease severity, as outlined in Table 3 (Gregory, 2016; Power et al., 1995; Thorel et al., 2020).

Medical management

Medical treatment of acute ocular involvement in SJS /TEN is directed toward aggressively reducing inflammation with systemic immunosuppression and/or topical steroid therapy depending on the severity of the disease. Sotozono et al. (2009) reported that early topical steroid use resulted in significantly better visual outcomes in a study of 94 patients with SJS. Additionally, aggressive hourly topical lubrication with preservative-free artificial tears is necessary to dilute the concentrations of proinflammatory agents and support epithelial healing (Jain et al., 2016).

Once membranous conjunctivitis occurs or the corneal and/or conjunctival surface develop epithelial defects, then additional, more aggressive intervention with amnionic membrane tissue (AMT), which contains anti-inflammatory components and growth factors, is necessary to control inflammation.

Ocular procedures in acute SJS/TEN

A commercially available cryopreserved human AMT suspended over a ring (Prokera-Slim Corneal Bandage, Biotissue Inc., Miami, FL) can be inserted at bedside or the clinic to protect the cornea or help heal epithelial defects (Fig. 3). The ring is replaced if the AMT dissolves and inflammation persists. Although easy to use, the

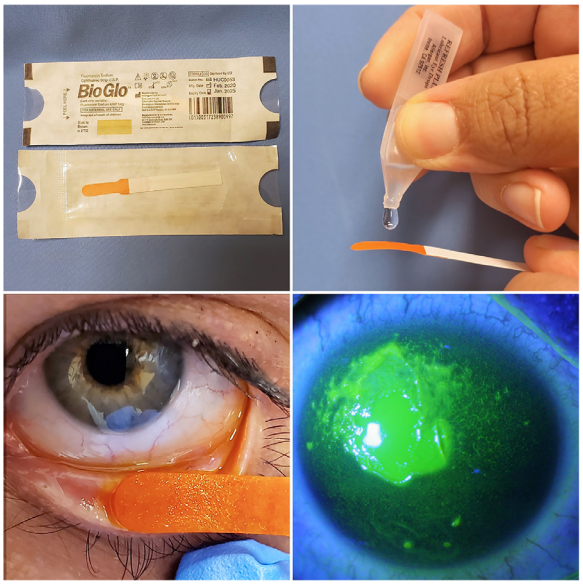

Fig. 2. Fluorescein staining of the ocular surface. A sterile fluorescein strip is moistened with artificial tears or saline solution and then used to touch the lower lid conjunctiva to release fluorescein. After a few blinks, the ocular surface is evaluated for epithelial defects on the conjunctiva and cornea (bottom right) using a blue light filter. The fluorescein stain is not toxic to the surface.

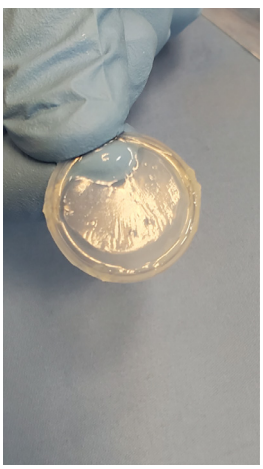

Fig. 3. Commercially available amnionic membrane disc suspended over a ring (Prokera Slim, Biotissue, Miami, FL) can be inserted into (and removed from) the inflamed eye at bedside or the clinic.

AMT ring does not cover the entire ocular surface and may not prevent symblepharon (adhesion of conjunctival surfaces) formation in noncovered areas (Shay et al., 2010).

In severe cases, early application of AMT with cryopreserved tissue (Amniograft, Biotissue Inc.) is recommended to completely cover the ocular surface from above the lid margins inside the lids and over the cornea. This procedure can be performed at bedside or in the operating room and can be repeated every 14 days until the inflammation resolves (Gregory, 2011; Ma et al., 2016; Saeed et al., 2020; Shay et al., 2009). Several case series have shown that early intervention with AMT (preferably within 5 days of onset of symptoms) can abate symblepharon formation and fornix foreshortening, promote epithelial healing, and result in good visual outcomes (Araki et al., 2009; Gregory, 2016; Hsu et al., 2012; Kohanim et al., 2016a; Shammas et al., 2010; Shanbhag et al., 2020b; Shay et al., 2010). Therefore, early consultation with ophthalmology is strongly recommended.

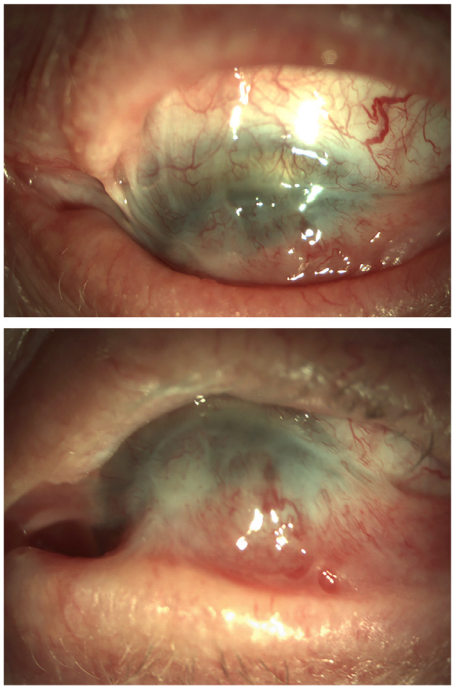

Fig. 4. (A) Symblepharon formation in a patient with chronic Stevens–Johnson syndrome showing conjunctivalization of the cornea, scarring, and loss of inferior conjunctival fornix. (B) Loss of motility on upward gaze (photograph courtesy of Dr. Joseph Pasternak).

Subacute ocular SJS/TEN

The subacute stage of the disease is characterized by chronic inflammation, severe dryness, and eyelid inflammation (Gurumurthy et al., 2018; Jain et al., 2016). Aggressive lubrication, fitting with a fluid-filled scleral contact lens to protect the cornea, and meticulous eyelid hygiene are important to avoid mechanical shearing and further damage to the ocular surface (Di Pascuale et al., 2005; Tougeron-Brousseau et al., 2009). Importantly, Yoshikawa et al. (2020a) reported progression of chronic disease in 33.3% of the eyes of patients with SJS/TEN followed over 5 years. This finding underscores the importance of early referral to an ophthalmologist for long-term management of inflammation, dry eye disease, and vision preservation in patients with SJS/TEN.

Chronic ocular sequelae of SJS/TEN

Chronic profibrotic inflammation starts approximately 8 weeks after initial onset and is observed in 35% to 50% of patients with SJS/TEN. Chronic cicatricial changes include symblepharon formation, trichiasis, eyelid margin rotation, and keratinization in up to 70% of patients, loss of MG in up to 79% of patients, scarring of LG ductules, loss of accessory LG, loss of mucin-producing goblet cells, loss of GF, abnormal corneal nerves, and LSC deficiency with inability to regenerate the corneal epithelium, resulting in loss of vision (Di Pascuale et al., 2005; Gurumurthy et al., 2018; Iyer et al., 2020; Kohanim et al., 2016b; Lekhanont et al., 2019; Nelson and Wright, 1984; Singh et al., 2021a; Sotozono et al., 2018; Ueta, 2018; Ueta and Kinoshita, 2010; Vera et al., 2009; Williams et al., 2013; Yang et al., 2016; Yoshikawa et al., 2020a; Fig. 4). Visual rehabilitation in these patients encompasses multiple surgeries, including removal of keratinization and salivary gland, mucous membrane, LSC, and corneal transplantations (Kohanim et al., 2016a; Lopez-Garcia et al., 2011).

End-stage SJS/TEN results in corneal blindness and a long process of ocular-surface reconstruction with implantation of a keratoprosthesis. However, the prognosis for good vision and prosthesis retention after surgery in patients with SJS/TEN is lower compared with other severe ocular-surface diseases (Sayegh et al., 2008).

Conclusion

The vulvovaginal and ocular mucosal surfaces are affected in the majority of female patients with SJS/TEN. Prevention of mucosal scarring is essential for the quality of life of survivors. Early and daily examination, grading, aggressive treatment of the vulva and ocular surface, as well as long-term follow-up of female patients with SJS/TEN with a dermatologist, ophthalmologist, and gynecologist are necessary to treat ongoing chronic progressive mucosal surface inflammation, minimize devastating long-term sequelae, and monitor for gynecologic neoplasia.

Conflicts of interest

None.

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Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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