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Original article

The chronic phase of Stevens-Johnson syndrome and toxic epidermal necrolysis: beyond skin and eyes

B Thanushah[1], N Thamilvannan[2], U S N Ranmohottige[3], B G S Ransimali[4]

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, potentially fatal drug reactions characterized by widespread blistering and separation of the skin and mucous membranes. While the immediate complications of SJS/TEN are well understood, growing awareness highlights that survivors can face lingering effects, some of which result in significant long-term health issues. Most studies on long-term effects have focused on skin and eye complications, but other internal organs, such as the respiratory and gastrointestinal systems, may also be impacted. Additionally, psychological consequences, stemming from the trauma of severe skin damage, are often seen. A thorough understanding of the chronic phase of SJS/TEN is vital for healthcare providers overseeing the care of patients recovering from the acute stage. This report describes two cases of TEN that involve long-term mucosal scarring and liver complications, showcasing the complexities of post-acute recovery in these individuals.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, potentially fatal drug reactions marked by widespread mucocutaneous blistering and the loss of epithelial layers. These conditions exist on a severity continuum: SJS involves less than 10% body surface area (BSA) detachment, whereas TEN results in over 30% BSA detachment. Cases with 10-30% BSA detachment are categorized as SJS-TEN overlap.

Although rare, occurring in 1-2 cases per million people, SJS/TEN is a life-threatening condition. While the immediate complications are well-established, there is growing recognition that survivors may experience delayed effects, some of which can lead to significant long-term health issues. Much of the research on the lasting impacts of SJS/TEN centers on skin and eye complications, though other organs such as the respiratory and gastrointestinal systems can also be affected. Additionally, psychological effects stemming from the trauma of extensive skin damage are common. A comprehensive understanding of the chronic phase of SJS/TEN is crucial for clinicians treating patients in the post-acute phase.

This article discusses two cases: one involving a TEN patient who continues to experience ongoing skin and mucosal issues, and another with an SJS-TEN overlap, complicated by drug-induced liver injury, leading to persistent cholestasis and potential chronic liver cell damage.

Case 1

A 24-year-old previously healthy female from a suburban area of Batticaloa was admitted to Teaching Hospital, Batticaloa with a 3-day history of skin peeling, erosions, and painful oral and genital ulcerations, along with red eyes and eye discharge. One week prior to her admission, the patient self-medicated with an antibiotic and possibly NSAIDs for symptoms of fever and cough. She continued the medications for 5 days. Four days after starting the treatment, skin and mucosal lesions began to appear.

Upon admission, 80% of her body surface area was covered with atypical dark to violaceous targetoid lesions and erosions, and she exhibited a positive Nikolsky sign. Her eyes were oedematous, reddened, and discharging purulent material. Both her oral and genital mucosa were severely eroded with discharge. Given the severity of her condition, the patient was immediately started on intravenous immunoglobulin (IVIg) therapy, along with supportive care, including nasogastric (NG) tube feeding. The eye complications were managed by an ophthalmologist.

While her cutaneous lesions gradually improved, the mucosal lesions took longer to heal. To aid in mucosal healing, the patient was treated with platelet-rich plasma (PRP) and autologous serum. Fortunately, she did not develop any other organ involvement, which is often a concern in such severe cases.

[1,2]*Consultant Dermatologist,* [3]*Registrar in Dermatology,* [4]*Senior Registrar in Dermatology, Teaching Hospital Batticaloa, Sri Lanka.*

Correspondence: BT, e-mail: thashahnu@yahoo.com

However, despite the improvement in skin lesions, the patient continues to suffer from long-term complications. Four years after the onset of her drug-induced reaction, she still experiences persistent erosive vaginal mucosa, vaginal stenosis, and scarring. Additionally, she has sustained nail destruction, pterygium formation and anonychia, loss of eyelashes, mild photophobia, and multiple atrophied facial scars.

She is undergoing treatment with an eye surgeon for her dry eyes and related complications, and with a gynecologist for erosive vaginal lesions accompanied by scarring. She is using topical epidermal growth factor for vaginal tissue regeneration and is awaiting plastic surgery reconstruction for scar tissue and vaginal stenosis. For facial scarring, she has started treatment with a low-setting fractional CO_2 laser.

Besides, she has low self-esteem and is very stigmatized since all this time she has not been able to enter into married life as a result of such severe vaginal erosions and scarring. These have had such a profound psychosocial effect on her life, further complicating the emotional and psychological stress she has gone through.

This case underscores the devastating long-term cutaneous and mucosal consequences of SJS and TEN overlap syndrome. Despite appropriate early intervention, the patient faces ongoing, chronic challenges, highlighting the need for long-term management and support to address the persistent sequelae and improve quality of life.

Figure 1.

Figure 2.

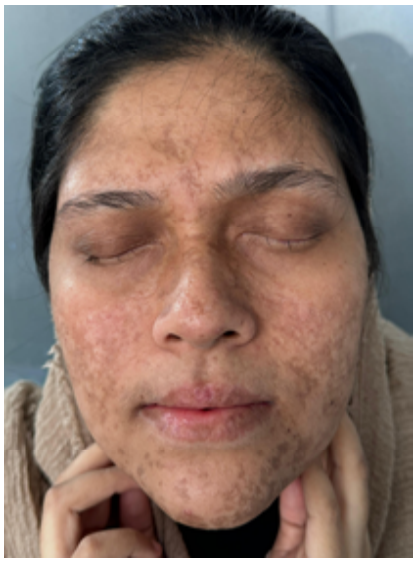
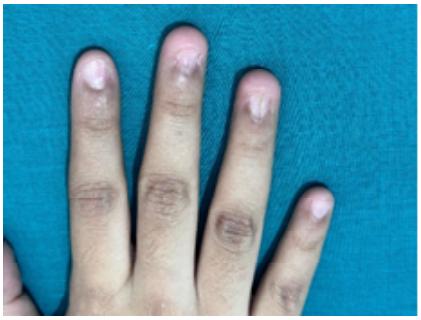


Figure 3.

Figure 1. *Erythematous to dusky discolouration of the facial skin with flaccid blisters, accompanied by ocular and oral involvement, on the day of hospital admission.*

Figure 2. *Three days after admission, epidermal detachment and erosions with necrotic surfaces on the face, along with severely inflamed, sticky eyelids and purulent discharge.*

Figure 3. *Four years after the onset of TEN, residual atrophic scars on the facial skin with areas of hyperpigmentation.*



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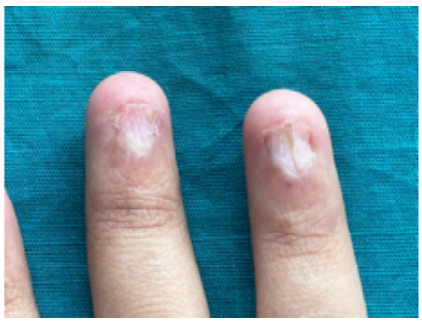

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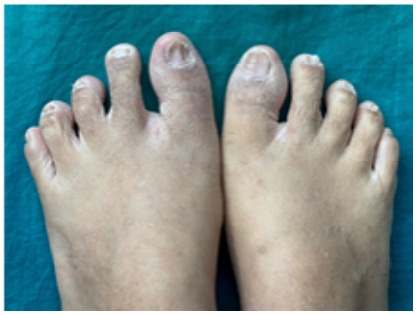

Figure 6.

Figure 4, 5, 6. *Chronic nail changes affecting both fingernails and toenails, including thinning, pterygium formation, longitudinal ridges, and anonychia.*

Figure 7.

Figure 8.

Figure 7. *Scarring of the eye lid margin,* **Figure 8.** *Loss of eye lashes.*

Case 2

A 48-year-old female from Batticaloa was admitted with a 5-day history of painful erythema and blistering of the skin involving the face, trunk, and hands. Additionally, she developed painful erosions in the mouth, eyes, and genitalia.

Ten days prior to admission, the patient experienced intermittent high-grade fever associated with arthralgia and myalgia. She did not report any respiratory, urinary, or gastrointestinal symptoms. On the third day of fever, she was prescribed oral ciprofloxacin, loratadine, domperidone, and mefenamic acid by a private practitioner. However, due to poor response and the onset of eye pain and discharge, she was continued on oral ciprofloxacin, azithromycin, and ciprofloxacin eye drops for an additional two days.

Despite the resolution of fever, the patient developed generalized pruritus, yellowing of the eyes (jaundice), dark urine, and painful blistering eruptions over her face, trunk, and hands, along with painful erosions in the oral, ocular, and genital mucosae. Within two days of worsening symptoms, she was treated with intravenous (IV) dexamethasone for 5 days at a private hospital but showed no significant improvement.

As a result, she was admitted at Teaching Hospital, Batticaloa, five days after the onset of skin lesions for further evaluation and management.

The patient has no significant past medical or surgical history and has no known drug or food allergies.

On admission, the patient was afebrile but deeply icteric. She was not pale and had no flapping tremors or ankle edema. Her abdomen was soft, non-tender, and without organomegaly or free fluid. The skin examination revealed cutaneous erosions, necrosis, and atypical targetoid lesions involving 20-30% of body surface area. There was also oral, ocular, and genital mucosal involvement. These findings were consistent with Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS-TEN) overlap syndrome. A systemic examination did not reveal any additional abnormalities.

The clinical presentation was consistent with SJS-TEN overlap syndrome, complicated by drug-induced liver injury. The patient was started on IV immunoglobulin (IVIg) 2g / kg over 5 days, along with oral prednisolone 50 mg daily, as advised by the Dermatologist and Gastroenterologist. Additional oral medications included ursodeoxycholic acid (UDCA) 300 mg four times daily, calcium lactate 1 tablet daily, omeprazole 20 mg twice daily, cholestyramine 2 mg daily, and Vitamin D 6000 IU weekly.

Her skin and mucosal lesions improved gradually, and liver enzymes began to normalize, although bilirubin levels remained elevated.

A liver biopsy was performed, and the pathology report revealed moderate mixed inflammatory infiltrate, scattered eosinophils, dilatation of sinusoids, canalicular cholestasis, and lobular steatosis, consistent with drug-induced liver injury.

Current Status and Plan: The patient continues to receive care from the Gastroenterologist for her persistent cholestasis and is being evaluated for Infliximab therapy as a potential treatment to prevent permanent liver injury. She remains on regular IVIg therapy as part of her ongoing management.

This case highlights a typical presentation of SJS-TEN overlap syndrome, complicated by drug-induced liver injury. The patient has been successfully managed with IVIg and corticosteroids, resulting in gradual improvement in both her dermatologic and hepatic symptoms. However, cholestasis and cholestatic pruritus remain unresolved even four months after the onset of drug induced liver injury. The patient will continue follow-up to monitor liver function, skin healing, and potential long-term sequelae. Future management will include ongoing IVIg therapy while closely monitoring her cholestatic status. If no improvement is achieved with IVIg, Infliximab will be considered as the next therapeutic option.

Figure 9.

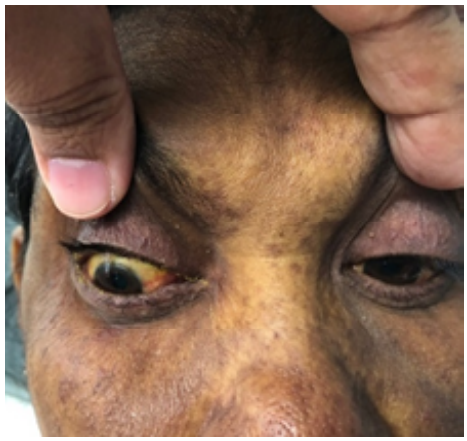

Figure 10.

Figure 11.

Figure 9. *Purpuric and necrotic lesions on the face and eyelids, along with involvement of the ocular and oral mucosa, during the acute presentation.*

Figure 10. *Deep jaundice (icterus) due to cholestasis, observed 4 months after the onset of SJS-TEN overlap.*

Figure 11. *Hyperpigmentation affecting the facial skin, accompanied by severe photophobia.*

Discussion

SJS and TEN are rare but severe drug-induced reactions that cause widespread skin and mucosal blistering, often leading to significant morbidity and mortality[2,4]. While the acute phase of these conditions is well-documented, growing recognition highlights the long-term complications survivors may face, which can affect various organ systems and significantly impact quality of life[1,7]. These complications include ongoing dermatological, ocular, gastrointestinal, and psychological issues, necessitating comprehensive care and long-term follow-up for those recovering from the acute phase of SJS/TEN[1,6,7].

Skin-related long-term effects

Dermatological complications are among the most common and significant long-term effects following SJS/TEN. The prevalence of these complications can vary greatly, impacting on the Dermatology Life Quality Index (DLQI), with rates ranging from 23% to 100%[7].

Nail abnormalities

Up to 50% of SJS/TEN survivors experience nail changes, such as onychomadesis (nail shedding), which can occur weeks after the acute episode[1,7]. In some cases, nail loss is permanent. When nails regrow, they often present with abnormalities like ridging, pterygium formation, dystrophy, cicatricial anonychia, and pigmentation changes. The extent of nail involvement is more common in patients with TEN or SJS/TEN overlap than those with isolated SJS[1,7].

Pigmentary changes

Post-inflammatory hyperpigmentation and hypopigmentation, either separately or in combination, are common after SJS/TEN[1,7]. Although these changes may improve over time, they can persist, causing significant distress. In regions like Sri Lanka, where people typically have darker skin types, post-inflammatory hyperpigmentation is more common. Intense pulsed-light therapy has shown some effectiveness, and PICO laser combined with topical agents is often considered the best approach for treating hyperpigmentation in patients with skin type IV or darker[7].

Abnormal scarring

Most skin lesions caused by SJS/TEN heal without scarring, but in 10-40% of cases, atrophic, hypertrophic, or keloid scars form[1,9]. Risk factors for abnormal scarring include prolonged immobility, skin pressure, secondary infections, and surgical interventions such as burn debridement or skin grafting. These factors, combined with disrupted expression of growth factors, can result in atypical scarring patterns. Fractional CO_2 lasers can be used to treat atrophic scarring, and targeted therapies should be tailored depending on the type and location of the scars[9].

Eruptive moles

Eruptive melanocytic naevi, or sudden clusters of new moles, can appear in up to 20% of SJS/TEN survivors, usually between 3 weeks and 3 years following the acute episode[7]. This phenomenon is believed to be linked to changes in the skin regeneration environment after SJS/TEN, although the exact cause remains unclear. Fortunately, these naevi are typically benign and generally require minimal intervention[7].

Additional cutaneous manifestations

SJS/TEN survivors may experience other skin-related issues, including telogen effluvium (hair loss), chronic pruritus, hyperhidrosis, and photosensitivity[1,7,12]. Rarely, heterotopic ossification can occur within 1-2 months of the acute episode, leading to joint contractures[12].

These long-term dermatological issues emphasize the need for regular follow-up care to manage and alleviate ongoing skin complications in SJS/TEN survivors[1,7].

Ocular sequelae

Chronic eye problems are among the most debilitating long-term effects of SJS/TEN, affecting 20-75% of individuals who survive these conditions[6,8]. Visual impairment can arise even after the acute phase, though it may also develop in cases where the eyes were not initially affected. These complications stem from a range of factors that vary depending on the specific structures of the eye involved[1,6]. During the acute phase, severe inflammation, the formation of pseudomembranes, and corneal epithelial defects can damage the ocular surface. Additionally, damage to conjunctival goblet cells and reduced mucin production compromise tear film stability, which is essential for clear vision. The loss of corneal stem cells further impedes the healing process. Scarring in the conjunctiva and eyelid margins can lead to issues such as symblepharon, ankyloblepharon, ectropion,

and entropion, which can result in persistent corneal erosion and eventual vision loss[1,6,7].

Prevention and management of complications

Preventing long-term eye complications after SJS/TEN is still not fully understood, and there is no conclusive evidence that treatments like intravenous immuno-globulin (IVIg) or systemic corticosteroids can effectively reduce chronic ocular problems[6]. However, early intervention with amniotic membrane transplantation (AMT) has shown promise in preventing ocular complications[7]. When performed within 2 weeks of ocular involvement, AMT can help reduce inflammation, promote healing, and prevent scarring[6,7]. Despite such interventions, the restoration of the ocular surface in SJS/TEN patients tends to be less successful compared to other causes of ocular surface failure[7].

Management of chronic ocular problems

The treatment of chronic ocular sequelae primarily involves the frequent use of non-preserved artificial tears to maintain moisture and alleviate dryness[1,6]. Scleral lenses may also help to prevent tear evaporation and reduce mechanical trauma to the ocular surface. Systemic immunosuppression might be used to control conjunctival inflammation, although its effectiveness can vary. If abnormal eyelid anatomy contributes to corneal damage, surgical correction may be necessary, and trichiasis (misdirected eyelashes) can be treated by removing the problematic eyelashes. Surgical procedures, such as limbal stem cell transplantation, AMT, and corneal transplants, may be required in severe cases, but their success rates in SJS/TEN patients are often limited[1,6,7]. Continuous ophthalmologic follow-up is critical, as new eye problems may arise months after the initial acute episode, and ongoing care is essential for managing these long-term complications[1,6,7].

Oral and dental sequelae

Oral mucosal involvement during the acute phase of SJS/TEN can cause significant long-term complications[1,12]. Mucosal lesions such as erosions, ulcers, and synechiae may persist after the acute episode, and oral ulcers may become recurrent. A significant number of survivors experience a form of sicca syndrome, with reduced saliva production and altered saliva composition, which can lead to dental issues such as gingivitis, periodontitis, and caries. In childhood cases, dental development may be affected, resulting in anomalies like dental agenesis, root abnormalities, and short roots[12]. These long-term oral sequelae emphasize the need for continued dental care and monitoring[12].

Pulmonary sequelae

Respiratory issues affect around 40% of SJS/TEN patients during the acute phase, with specific problems like bronchial epithelium sloughing in 25% of cases, alongside non-specific complications such as pulmonary edema, atelectasis, and pneumonia[12]. In survivors, long-term respiratory issues include conditions like interstitial lung disease, airway obstruction, bronchiectasis, and bronchitis, with bronchiolitis obliterans (BO) being the most frequent[12]. BO arises from injury to the airway epithelium, leading to scarring, fibrous tissue buildup, and ciliary dysfunction, which predisposes to further infections and airway narrowing. The condition primarily affects peripheral bronchi and bronchioles, causing progressive shortness of breath and severe obstruction[12].

BO is particularly common in children and often linked to mycoplasma infections, though it's unclear whether mycoplasma is a contributing factor or just more prevalent in pediatric cases[12]. Adult pulmonary sequelae are less frequent, possibly due to higher mortality in adults with pulmonary involvement during the acute phase[10,11]. A study of 32 SJS/TEN survivors revealed that over 50% had abnormal pulmonary function tests (PFTs) two months after recovery, with most showing impaired alveolar diffusion[11]. However, over 90% were asymptomatic. Long-term PFTs also showed continued abnormalities in alveolar diffusion, but obstructive lung diseases were rare in adults[11].

Urogenital/gynaecological sequelae

Genital involvement occurs in 70% of acute SJS/TEN cases, with 28% of survivors developing chronic urogenital issues, typically around eight months post-acute phase[1,7]. Adhesions are the most common issue, affecting various parts of the female genitalia and causing pain during intercourse or even complete vaginal fusion, leading to haematocolpos. Other gynaecological complications include vaginal adenosis, endometriosis, and persistent genital ulcers. Surgical interventions for these issues include procedures like nymphoplasty and vaginal dilation, though responses vary. Early prevention of adhesions may include the use of vaginal molds during the acute phase and menstrual suppression in cases with severe genital lesions[1,7].

Gastrointestinal and hepatic sequelae

GI involvement is rare but can lead to esophageal strictures, which may appear months to years after the acute episode and can be treated with endoscopic dilation[7]. Persistent ileal ulcers can cause diarrhea and malabsorption, potentially requiring parenteral nutrition or surgery. Additionally, cholestasis and vanishing bile duct syndrome (VBDS) are rare but serious complications, characterized by progressive bile duct loss. Treatment for VBDS may include medications like infliximab and corticosteroids, but liver transplantation might be necessary in severe cases[7].

Renal sequelae

Around 20% of SJS/TEN patients experience acute kidney injury (AKI), with proteinuria occurring in 60% of cases[10]. A small percentage of these patients may require long-term dialysis. Additionally, some survivors may develop chronic renal issues, including glomerulitis or long-term renal insufficiency, though the relationship between the disease and long-term renal function remains unclear[1,10].

Psychiatric and psychosocial sequelae

Survivors of SJS/TEN are at higher risk of mental health issues such as depression and post-traumatic stress disorder (PTSD), especially after intensive care and burn injuries[11]. Many survivors face challenges returning to work or modifying their job roles. Psychological assessments and support are critical in the long-term management of these patients[1,11].

Long-term survival

Longitudinal data from the RegiSCAR study revealed that mortality in SJS/TEN remains high post-acute phase, with 23% dying within 6 weeks, 28% by 3 months, and 34% by one year[3]. Mortality risk in survivors is linked to the severity of the acute disease, older age, and pre-existing health conditions. A higher SCORTEN score and delays in specialized treatment are also poor prognostic indicators for long-term survival[3,5].

Conclusion

Survivors of SJS/TEN can experience a broad range of chronic complications that extend beyond the skin and mucous membranes. Comprehensive follow-up care across multiple specialties, including dermatology, ophthalmology, respiratory medicine, urology/gynaecology, gastroenterology, and psychiatry, is necessary to address these long-term issues. A structured, multidisciplinary approach is crucial for managing the lasting effects of the disease.

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