Review Article

Current Trends in the Management of Stevens–Johnson Syndrome: A Call for a Paradigm Shift in Ophthalmic Care in Nigeria

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Abstract

Stevens–Johnson syndrome (SJS) is a severe blistering mucocutaneous disorder, which affects the skin and at least two mucous membranes that very often includes the eyes. The ophthalmic complications, though considered the most devastating of all the complications of the disease in survivors, are often a time the last to be attended to, with consequent life-changing sequelae. Medical therapy has been the mainstay of ophthalmic care in our locality, and these have not been shown to improve the long-term outcome of the disease. Glass rod synechiolysis, previously practiced in some centers, has been largely abandoned. Appropriate proactive interventions such as lubrication, topical antibiotics, and steroids are advocated in the acute phase. Surgical management to remove the membranes and the use of improvised symblepharon rings prevent adhesions. Amniotic membrane grafting or mucous membrane grafting for lid margin keratinization and forniceal scarring if implemented will also take advantage of a window of opportunity to ameliorate the severity of the long-term sequelae requiring more specialized and expensive interventions for vision restoration. The critical role of the ophthalmologist in the management of patients with SJS for the prevention of corneal blindness, therefore, cannot be overemphasized.

Keywords: Mucocutaneous disorder, Stevens–Johnson syndrome, toxic epidermal necrolysis

Introduction

Stevens and Johnson first described an acute blistering inflammatory mucocutaneous disease in 1922 in two children. This disease involved severe erosions in the mouth, eyes, and skin with blindness as the residual sequelae.[1] Subsequently, several authors have described similar presentations without clear-cut definitions regarding the disease entities.[2-8] Bastuji-Garin *et al*. proposed a classification and case definition for Stevens–Johnson syndrome (SJS) in 1993,[9] which has become widely accepted in the literature.[10-17] The severe cutaneous adverse reactions (SCAR) study group in seeking to validate this classification, established that erythema multiforme major (EMM) was a distinct disorder, whereas SJS, SJS–toxic epidermal necrolysis (SJS–TEN), and TEN were a severity spectrum of the same disease.[18] This observation is widely accepted in the literature.[16,19-22] The original cases described by Stevens and Johnson clinically fit the description of EMM. The outcome of long-term ocular complications in survivors is highly dependent on interventions during the early phase of the disease, because an adequate multidisciplinary management of the disease manifestations according to current best practices[13] is very crucial.

SJS and TEN pose a serious threat to life in the acute phase, and is followed in survivors by blinding cicatricial ocular complications. In the acute phase, due to its high morbidity and mortality rate, the focus of clinical care is on the preservation of life, and, often, little or no attention is given to the inflammatory changes occurring in the eyes.[14]

Etiopathogenesis

The skin is a two-layered structure consisting of the external epidermis—keratinizing stratified squamous epithelium—

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and the inner dermis separated from each other by a collagen-rich basement membrane.[23] Keratinocytes are proliferative cells located in the basal layer of the epidermis that maintains a constant supply of new cells to the rapidly transiting squamous epithelium.[23] The basal layer is bound to the basement membrane by hemidesmosomes, thus maintaining the integrity of the skin.[10,24] The mucous membranes of the mouth, eyes, respiratory tract, and urogenital tract have a similar structure but are lined by the non-keratinizing stratified squamous epithelium or columnar epithelium.[23] Their affectation is based on a similar pathogenesis. This group of blistering mucocutaneous diseases are type IV delayed hypersensitivity reactions, in which the Th1 (T-helper cells type 1) attack and destroy the keratinocytes by inducing massive apoptosis in these cells. This results in a failure of the hemidesmosomal attachments, which are epithelial detachments from the basement membrane, and serous fluid dissecting a plane between them over time to form bullae, which slip away and rupture, leading to a massive de-epithelialization across the body surfaces and mucous membranes.[10] The massive keratinocyte apoptosis renders the epidermis and epithelial surfaces disconnected from their vascular bed with resultant necrosis, inflammation, and sloughing.[10,15]

Epidemiology

The blistering mucocutaneous diseases are rare conditions with an estimated incidence of 1–6 cases per million person-years for SJS and 0.4–1.2 cases per million person-years for TEN.[11,25] About 50–88% of the patients with SJS/TEN have their eyes affected in the acute phase.[15] Due to the rarity of the disease, there are only a small number of patients per year per facility, with the result that large, well-designed studies of the disease are difficult to execute.[26] In addition, not many healthcare practitioners are confident in the diagnosis and management of the disease.[27] Mortality for SJS is estimated at less than 10%, rising to 30% with TEN; while, the mean mortality rate for the entire spectrum is 22%.[28] Jongkhajornpong *et al*. reviewed 89 cases over a 10-year period and found chronic sequelae on long-term follow-up in 49.44% of the cases and severe visual impairment in 25.84% of the cases.[29] In a report from Cape Town, 90% of all patients with SJS had chronic sequelae, whereas 17% had moderate-to-severe visual impairment from corneal opacification sequel to lid margin abnormalities.[30] Yang evaluated the Korean health insurance database and found that the most common long-term complication in survivors was ocular (43%) in nature followed by urethral (5–9%).[31]

Differential Diagnosis

EMM presents with the classical target lesions with affectation of only one mucous membrane (commonly oral) without a prodrome. It often resolves within 2 weeks without significant sequelae.[32,33] Staphylococcal scalded skin syndrome occurs in children preceded by conjunctivitis and sore throat. Bullous eruptions result from exotoxin release and are exquisitely tender, affecting the flexural areas of the skin.[34] Bullous systemic lupus erythematosus is an uncommon presentation of systemic lupus erythematosus (SLE). Widespread vesicobullous eruption occur on the upper half of the body and the mucosa along with the classical features of SLE.[35] Linear immunoglobulin A bullous dermatosis is a rare autoimmune mucocutaneous disorder caused by immunoglobulin A autoantibodies produced against several different antigens in the basement membrane zone. Clinically, it is characterized by tense vesicles or bullae, which on histopathological examination demonstrate subepidermal blister with a predominantly neutrophilic infiltrate. A smooth, linear pattern of immunoglobulin A deposition in the basement membrane zone on direct immunofluorescence is considered the gold standard for establishing a diagnosis. The treatment consists of dapsone or sulfapyridine. The authors report a 60-year-old woman who presented with pruritic erythematous patches and plaques on her trunk, back, and legs without blisters. The woman was diagnosed with eczema for several months with no response to prior treatments. A biopsy was performed, which was consistent with linear immunoglobulin A bullous dermatosis and later confirmed by direct immunofluorescence studies. The authors present this case to increase awareness regarding this rare disease, which could manifest in a nonclassical, nonblistering fashion.Linear immunoglobulin A bullous dermatosis is a rare autoimmune vesiculobullous disease, which may affect children or adults.[36] Mucous membrane pemphigoid is an autoimmune disease, which presents as subepithelial bullae affecting mostly the oral mucosa and conjunctiva with significant scarring as sequel. Involvement of the skin is mostly limited to the head, neck, and superior trunk.[37]

Paraneoplastic pemphigus is a severe mucocutaneous disease associated in most cases with B-cell lymphoproliferative disorders and presents with bullous eruptions, an altered epidermis on histological examination, and complement deposition in the basement membrane along with circulating autoantibodies. The common underlying malignancies are non-Hodgkin's lymphomas and chronic lymphatic leukemias.[38] Generalized bullous fixed drug eruption is a vesicobullous disease associated with increased eosinophil infiltration and macrophages on skin biopsy. It involves at least three anatomical sites involving less mucosal surfaces than SJS.[39] Acute graft versus host disease follows stem cell transplantation as donor immune cells reaction against host tissues. The disease is suspected if a recipient presents with a rash, blisters, abdominal pain, nausea, vomiting, or elevated liver function tests within the first 3 months of transplantation.[40-44]

Predisposing Risk Factors

Infections such as herpes simplex, recent respiratory tract infection in children, and mycoplasma pneumonia have been implicated as triggers for the development of EMM, and

drugs play a predominant role in the SJS–TEN spectrum.[18] Some of the strongly implicated drugs include antibacterials (sulphonamides, aminopenicillins, cephalosporins, quinolones, and tetracyclines), anticonvulsants (phenytoin, phenobarbitone, carbamazepine, and valproic acid), nonsteroidal anti-inflammatory drugs, and others such as allopurinol, acetaminophen, and highly active antiretroviral therapy.[45,46] HIV infection, cancer, and collagen vascular diseases were more associated with SJS–TEN spectrum than EMM.[18,47]

Classification and Clinical Features

These disorders are classified based on the pattern of the skin lesion, the distribution, and the extent of cutaneous involvement, namely the following:

(1) EMM is now considered a distinct clinical entity from SJS/TEM spectrum.[9,48] EMM is characterized by an acral distribution (preference for the extremities) of classical target lesions, which subsequently form bullae, rupture, and expose the underlying dermis. The target lesions have a round shape, well-defined borders, with three concentric zones—a central hyperemic core, a circumscribed clear area, and this is surrounded by a hyperemic ring.[12] The extent of body surface involvement is between 1 and 10% (commonly 1–2%). The SCAR study found patients with EMM to be younger and more commonly of the male gender, with a higher recurrence rate of the disease, only one mucous membrane involvement, and likelihood to have a respiratory tract infection. Association with cancer, HIV infection, or collagen vascular disease was unlikely.[18]

(2) The SJS/TEN spectrum is divided into the following three groups based on the extent of body surface involvement:
   (a) SJS: 1–10% (commonly 4–8%) with body surface area involvement, two or more with mucous membrane involvements, and association with recent herpes reactivation or mycoplasma pneumonia.[18]
   (b) SJS–TEN overlap: 11–29% with body surface area involvement, associated with recent drug use.[18]
   (c) TEN: body surface area involvement ≥30%, associated with recent drug use with mortality rates reaching 35%.[13,18]

The SJS/TEN spectrum does not have the classical target lesions seen in EMM. Rather there are flat atypical targets, which develop into bullae over time, with widespread truncal distribution; two or more mucous membrane surfaces are usually involved with a higher risk of mortality than EMM.

An estimation of the extent of body surface involvement can be performed using the simple Wallace rule of nines, wherein each upper limb is scored 9%, each lower limb is 18%, the chest and back are 18% respectively, the head is 9%, and the genitalia are scored 1%. Other more accurate scoring systems exist but are beyond the scope of this discussion.[49]

Nikolsky's sign is positive in both EMM and SJS/TEN spectra. To elicit the sign, the thumb is used to apply pressure on the affected skin, and the skin is rubbed gently. This movement causes the epidermis to easily slide off the dermis to expose its pink vascularized surface, as evidenced by the presence of dermal blood vessels. This is considered an important diagnostic sign in these conditions.[50] This sign is not pathognomonic, because it is positive in other blistering disorders.[12,27]

The Prodromal Phase

This phase is characterized by fever, sore throat, malaise, anorexia, a running nose, cough, and generalized body pains lasting up to a week.[10,15]

Manifestations in the Acute Phase

The acute phase follows within 2 weeks of the prodrome, with an inflammation of the skin and mucous membranes resulting in sloughing off of these epithelia. Ophthalmic involvement presents as hyperemia, bilateral conjunctivitis, conjunctival sloughing, or corneal ulceration and is noted in 60–100% of cases.[51-53] A contiguous or kissing ulceration of the palpebral and bulbar conjunctiva would result in adhesions that could later scar off as symblepharon. The involvement of the lid margins could also subsequently result in ankyloblepharon formation. The result would be poor tear distribution, globe restriction, and incomplete blinking.[13] The extent of the ocular involvement has not been shown to correlate with the severity of the systemic disease.[13,51,52]

Systemic involvement may affect the nail beds and result in loss/deformity of the nails. Sparing of the scalp is often noted.[15] Genital and ororespiratory mucosal involvements could in the long run result in strictures and respiratory difficulties, respectively. Classical histopathologic findings on skin biopsy at this stage would be necrolysis of the epidermis with monocyte infiltration of the dermis.[15]

Manifestations in the Subacute Phase

At this stage, the systemic disease is in remission with the skin lesions mostly healed, and the patient may have been discharged from admission.[14] There may be worsening of the red eye, for which the patient presents to the ophthalmologist. An examination may reveal dry eyes, corneal or conjunctival ulceration, trichiasis, irregular lid margins, and tarsal plates.[14] The ophthalmic involvement at this stage has been aptly described as a "smouldering, chronic cicatrizing conjunctivitis" with lid margin changes and trichiasis.[14]

Manifestations in the Chronic Phase

Chronic ocular complications occur in 20–80% of SJS/TEN survivors.[13,54] Ocular surface inflammation and ulceration may persist. Cicatrization may occur in the lacrimal glands with resultant failure of their secretory functions and the

development of aqueous tear deficiency. The destruction of the meibomian glands may occur, with an appearance of distichiatic lashes and resultant lipid layer deficiency.[14,54,55] Increasing goblet cell loss results in reduced mucin secretion and squamous metaplasia.[55] There may be scarring with the contracture of the tarsal conjunctiva causing entropion and trichiasis.[14,27,54] Keratin plaques are deposited at the lid margin, which loses its normal acute angle at the mucocutaneous junction to take up a rounded appearance.[14,55] Corneal damage results from microtrauma, which occurs at every blink from the abnormal lid margin. The chronic inflammation results in progressive limbal stem cell destruction with resultant keratinization of the entire ocular surface as seen in long-standing disease.[14,56] Sotozono *et al*. succinctly graded the extent and severity of the involvement of the cornea, conjunctiva, and eyelids. They considered the presence of superficial punctate keratopathy, the loss of the palisades of Vogt, epithelial defect, the conjunctivalization of the cornea, neovascularization, opacification, keratinization, conjunctival hyperemia, symblepharon, trichiasis, and changes in the mucocutaneous junction and the punctum. They concluded that the final visual prognosis depended on the severity of the ocular involvement.[57]

Current Management in Nigeria

In our locality, patients with SJS/TEN in the acute phase of the disease are managed primarily by the pediatricians and by the internal physicians. They may be nursed in an isolation ward with reduced external traffic under reasonably aseptic conditions. Infection control, wound care, and fluid and electrolyte balance are the mainstay of care. The involvement of other specialists may be limited to the ophthalmologist or any other as per the discretion of the managing physician. The ophthalmologist would examine the eyes for the presence of ulcers or synechiae, and treatment may include topical antibiotic drops and ointments. Glass rod synechialysis for any existing adhesions was practiced previously in some centers but has been largely abandoned. However, active appropriate surgical intervention in the acute phase is not the common practice. In addition, frequent glass rod synechialysis, as is the common practice locally, would trigger further inflammation in a disease propagated by chronic inflammation[12,14,54,55] and, therefore, should be discouraged.

Global Trends in the Management of Stevens–Johnson Syndrome and a Call for a Paradigm Shift in Ophthalmic Care in Nigeria

The goal of treatment is survival and recovery from the systemic disease as well as the prevention of cicatricial complications in the affected organ systems.[55] Management requires a prompt, interventional, multidisciplinary approach with a predominance of specialists in the different phases according to the specific needs of the patient.[13-15,27] In the prodromal phase, the course and outcome of the disease are probably unclear, and the disease is managed generally as a febrile illness.[58] With the onset of the acute phase, a diagnosis is made based on the history of drug use or respiratory infection, characteristic skin eruptions, and epithelial sloughing.[59] Multiple body systems are involved, and the patient could succumb to the disease from any of the systemic pathologies. In compliance with global best practices,[12,14,15] we recommend that these patients be admitted in a Burns Intensive Care Unit (BICU) under the care of a burns specialist (burns and plastic surgeon) as the primary physician. Care should be multidisciplinary from day one of admission,[15] with all the relevant specialists invited for initial assessment and to make recommendations for the primary prevention of the complications of the disease, early diagnosis and prompt treatment, the detection of any complications, and institution appropriate management.[12] A plastic surgeon, dermatologist, anesthetist, ophthalmologist, pediatrician, and physicians with experience in the management of these patients should definitely be on the team. Attention should be paid to fluid and electrolyte balance, the prevention or treatment of secondary infections, wound care, nutrition, and pain management. Other specialists should be invited to determine the extent of the involvement of the disease in these areas including the otorhinolaringologist, respirologist, dermatologist, gastroenterologist, gynecologist, and urologist.[16] Their interventions as needed in the acute phase will mitigate long-term complications in these systems. Nursing care should be by a specialized burns nurse.

The role of the ophthalmologist with requisite skills for the management of these patients is paramount, because the ophthalmic complications have been reported as the most devastating sequelae of the disease. Interventions in the early phases determine the extent and severity of the long-term ocular complications. This is one condition wherein "prevention is definitely better than cure."[14] Kohanim *et al*. described this as "a window of opportunity" at each stage of the disease to interrupt the vicious cycle of inflammation and scarring that will eventually result in complications that are far more difficult to reverse.[54] Ciralsky strongly recommended that these patients be managed by ophthalmologists who are conversant with the current standard of care in the interest of the patient.[60]

In the acute phase, (the period of admission in the BICU), the patient should be seen daily by an ophthalmologist with the aim of controlling inflammation, as well as preventing infection and symblepharon formation. The examination of the fornices and the staining of the entire ocular surface with fluorescein should be performed with the lids everted over a Desmarres retractor.[13] Discharge, debris, pseudomembranes, and true membranes should be gently removed using a cotton-tipped bud with a saline flush (topical anesthetic may be required).[14] The main stay of care is the liberal use of lubricants (preferably nonpreserved) every half to one hour. Prophylactic antibiotic drops four times daily and topical steroids have been reported to improve the outcome of care and have become an acceptable practice.[13,14,54] Topical steroid drops plus ointment for

the lid margin is recommended only after microbial keratitis has been excluded.[15] A symblepharon ring or a modified ring made from intravenous tubing as described by Ma *et al*. can be used with copious lubrication to prevent adhesions in the fornix.[61] As these patients are not admitted in the eye ward, it becomes the responsibility of the ophthalmologist to teach and demonstrate to the nurses in the BICU the method of appropriate application of ophthalmic medications, as well as to ensure an accurate charting of ophthalmic medications in his/her absence.

Amniotic membrane grafting in the acute phase of the disease has shown great promise and, currently, is advocated within the first 2 weeks of the onset of the disease for the patients who demonstrate a sloughing of the ocular surface (cornea, conjunctiva, or lid margins) or pseudomembrane formation. Several authors advocate a low threshold for amniotic membrane transplantation in the acute phase of the disease.[14,54,61] The aim is to cover the entire ocular surface, including the fornices, cornea, and the lid margin with the membrane. This tends to reduce ocular surface inflammation, form a scaffold for re-epithelialization, and prevent symblepharon formation, thus mitigating the long-term sequelae of the disease. Transplants can be repeated weekly throughout the period of active epithelial sloughing.[14] Human amniotic membrane (HAM) is being used in a few centers in Nigeria as commercially purchased dried HAM. The placement of amniotic membrane coupled with a modified symblepharon ring is a simple procedure that can be performed at the bedside under local anesthesia. Ma *et al*. published a detailed pictorial description of the procedure in 2016 using a modified symblepharon ring made from the tubing of a simple drip-giving set (intravenous tubing).[61] The advantage of the use of the modified ring is that it is fabricated to snugly fit into the patient's fornix unlike the customized ones such as Prokera (amniotic membrane plus symblepharon ring as a single unit), which may fall short of the depth of the fornix in some patients, allowing for the formation of symblephara in those areas.[13,61]

The subacute phase has the patient discharged from the BICU with a resolution of symptoms or, quite often, a persistent red eye. The ocular inflammation persists, triggering the onset of the cicatricial components. The scarring of the lacrimal glands, meibomian glands, and the three parts of the conjunctiva begins to set in. Resultant tear abnormalities commence, with the drying of the ocular surface setting up a vicious cycle of ocular surface inflammation and scarring. Corneal microtrauma results from dryness as well as rubbing of the keratinized lid margin on the cornea. This keratin should be scrapped off with the blunt side of a number 15 surgical blade until definitive treatment with mucous membrane grafting can be performed.[14] Limbal stem cell deficiency (LSCD) may set in with a resultant vascularization of the cornea. A scleral contact lens, for example, the prosthetic replacement of the ocular surface ecosystem (PROSE) lens, can be used to create a barrier between the lid margin and the cornea/limbus and, thus, prevent vascularization from LSCD.[14] They are commonly available in developed countries and significantly improve patient comfort, the drawbacks being the high cost (even abroad), nonavailability in our locality, not for overnight wear, and the constant risk of microbial keratitis. In the presence of significant symblepharon, these lenses cannot be fitted, because a tear lens cannot be formed.[62]

Urgent mucous membrane transplantation to replace the keratinized lid margin will interrupt this cycle and limit the progression of the corneal blinding complications. Iyer *et al*. reported the regression of corneal vascularization and improvement in visual acuity, the health of the ocular surface, as well as patient comfort following mucous membrane grafting in these patients.[63,64] Mucous membrane grafting is further beneficial in symblepharon release and fornix reformation in the event of foreshortening of the fornices.[64,65] Sufficient membrane can be harvested from the lips to cover the four lid margins. However, fornix reformation may require harvesting of the buccal mucosa as described by Jain *et al*.[14]

At the chronic phase, LSCD may result in conjunctivalization or dermalization of the cornea with resultant near-total vision loss. Schirmer's test is commonly zero, and the prognosis for corneal transplantation is very poor. These patients may benefit from a mucous membrane graft for fornix reformation if the fornices have been obscured by scarring. Visual rehabilitation would be dependent on the placement of a Boston or LVP keratoprosthesis with limited visual fields but improvement in navigational vision.[14] These procedures are often multistaged and highly demanding. The patient's expectations must be clearly evaluated to ensure that they are realistic. Psychological support is highly indicated in these patients, because the reality of vision loss can be very distressing.[14,27]

Conclusion

Early appropriate intervention with topical lubricants, antibiotics, and steroids, as well as a timely surgical debridement of the membranes and lid margin keratin, is the mainstay of treatment in the early phase of the disease to mitigate the appearance of chronic complications. Amniotic membrane transplantation in the acute phase should be performed whenever possible. Mucous membrane grafting and fornix reformation are very useful in interrupting the vicious cycle of this scarring disease. All these would help to prevent corneal blindness that would otherwise result from the natural course of the disease.

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Conflicts of interest

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