STEVENS–JOHNSON SYNDROME SECONDARY TO LAMOTRIGINE (MARIGOLD TABLET) OVERDOSE:

A Chronic, Complicated Case with Bilateral Ocular Involvement, Failed Skin Grafting, and Progressive Deterioration Over Fifteen Years

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Abstract : Stevens–Johnson Syndrome (SJS) is a rare, life-threatening mucocutaneous hypersensitivity disorder characterised by extensive epidermal detachment, severe mucous membrane erosions, and systemic inflammatory involvement. Drug-induced SJS carries a significant burden of morbidity and mortality, with anticonvulsants such as lamotrigine recognised among its most common precipitants. This case report documents the longitudinal clinical course of a 35-year-old female patient who initially developed SJS fifteen years ago following an overdose of lamotrigine (commercially marketed as 'Marigold' tablet), with progressive and currently worsening symptomatology. The patient presented with bilateral ocular involvement characterised by small papular lesions on the conjunctiva, blurring of vision in both eyes, and a history of failed left corneal surgery. Systemic features included elevated alanine aminotransferase (SGPT), elevated alkaline reserve (AZR), haematological abnormalities including low haemoglobin (10.1 g/dL) and relative neutropenia (40%), dry mouth, and persistent bilateral ocular irritation. A prior attempt at skin grafting was unsuccessful. Current pharmacological management includes Folitrax 20 mg tablet (methotrexate), Folvite 5 mg tablet, topical oral gel, and therapeutic eye drops. This report discusses the diagnostic criteria, pathophysiology, ocular complications, haematological implications, long-term sequelae, and current management strategies pertaining to this patient's condition, with reference to contemporary literature. The aim is to contribute to the growing body of evidence on chronic, refractory SJS cases and to highlight the critical importance of early recognition, cautious drug prescription, and multidisciplinary long-term care.

Keywords: Stevens–Johnson Syndrome; lamotrigine; drug hypersensitivity; ocular complications; toxic epidermal necrolysis; methotrexate; corneal involvement; chronic SJS; skin grafting failure.

I. INTRODUCTION

Stevens–Johnson Syndrome (SJS) is one of the most devastating acute dermatological emergencies encountered in clinical practice. Originally described by American paediatricians Albert Mason Stevens and Frank Chambliss Johnson in 1922, SJS was initially characterised as a severe mucocutaneous syndrome with systemic features. Over subsequent decades, it has been redefined and placed along a clinical spectrum that includes, at its most severe end, Toxic Epidermal Necrolysis (TEN). SJS involves epidermal detachment affecting less than 10% of the total body surface area (TBSA), while SJS-TEN overlap involves between 10% and 30% TBSA involvement, and TEN is characterised by detachment exceeding 30% TBSA [1]. The condition is now classified as a type IV hypersensitivity reaction primarily mediated by cytotoxic CD8+ T lymphocytes and natural killer (NK) cells that mount a destructive immune response against keratinocytes expressing drug antigens in the context of MHC class I molecules [2].

The epidemiology of SJS reflects its rarity but also its severity. Estimated incidence rates range from 1 to 6 cases per million population per year for SJS and from 0.4 to 1.2 cases per million per year for TEN [3]. Despite these low incidence figures, the overall mortality associated with TEN can reach 30–40%, while SJS mortality, though lower, still poses significant clinical risk, particularly when there is extensive mucosal involvement, ocular complications, or failure of standard therapeutic interventions [4]. The condition does not discriminate by age, sex, or ethnicity, although certain genetic predispositions—particularly HLA alleles—are known to significantly amplify the risk of drug-induced SJS/TEN in specific populations [6].

Drugs represent the primary aetiological agents in the vast majority of SJS cases. The list of implicated medications is extensive and includes anticonvulsants, sulfonamide antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), allopurinol, and certain antiretroviral agents [11]. Among anticonvulsants, lamotrigine holds a particularly notorious position as a causative agent. The risk of SJS associated with lamotrigine is dose-dependent and is significantly amplified when the drug is escalated too rapidly or when plasma concentrations exceed therapeutic thresholds, a scenario classically precipitated by intentional or accidental overdose [8]. The drug acts as a hapten or pro-hapten, binding to endogenous proteins and triggering an aberrant immune response in genetically susceptible individuals [2].

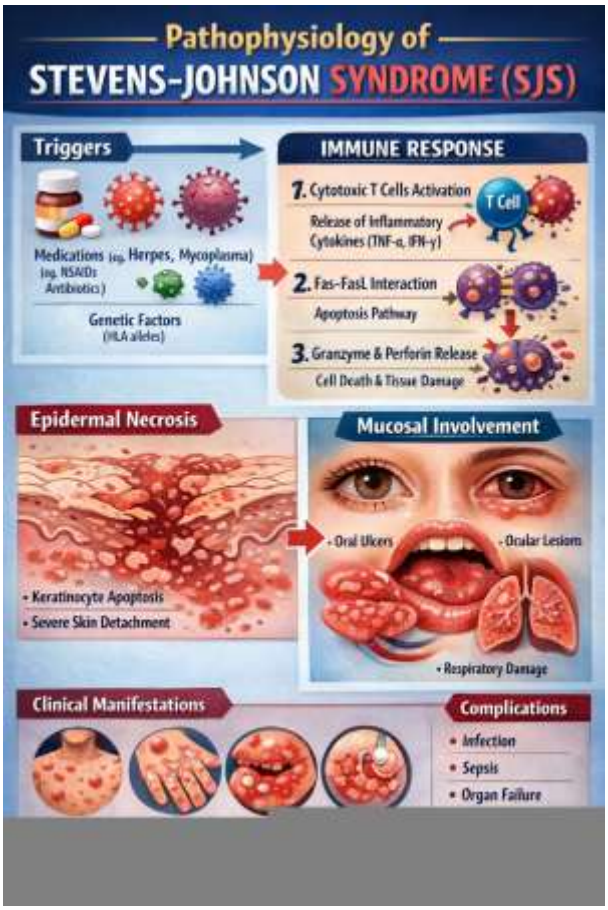

Figure 1. Pathophysiology of Stevens–Johnson Syndrome (SJS).

The clinical picture of SJS is dominated by the rapid onset of painful erythematous or purpuric macules that evolve into blisters and areas of denuded skin, accompanied by erosions of the oral, ocular, and genital mucosae [1]. Ocular involvement is particularly devastating and represents one of the most common long-term complications of SJS. The ocular sequelae of SJS include conjunctival scarring, symblepharon formation, corneal neovascularisation, limbal stem cell deficiency, and chronic dry eye disease, all of which can progress to permanent visual impairment or blindness [3]. These complications may persist and worsen long after the acute episode has resolved, creating a chronic disease burden that challenges both patients and clinicians [5].

Long-term management of SJS survivors with refractory or progressive disease remains a subject of considerable clinical debate. Immunosuppressive agents, including systemic corticosteroids and methotrexate, have been employed in managing both the acute phase and chronic sequelae [10]. Methotrexate (Folitrax), a folate antagonist with immunosuppressive and anti-inflammatory properties, has been utilised in some SJS cases to modulate the aberrant immune response, particularly where conventional therapies have failed. Supplementation with folic acid (Folvite) is standard practice alongside methotrexate to mitigate haematological and gastrointestinal toxicity [5].

Skin grafting is occasionally considered for patients with extensive denuded areas, though success rates in SJS/TEN are variable and often complicated by the underlying immunopathology [9]. Similarly, ocular surgeries including corneal transplantation may be attempted to restore visual function in patients with severe corneal damage, but these procedures carry a high risk of failure in the context of chronic ocular inflammation and limbal stem cell deficiency associated with SJS [3].

This case report presents a detailed account of a 35-year-old female patient with a confirmed diagnosis of SJS secondary to lamotrigine overdose, with disease onset fifteen years prior to the current presentation and progressive worsening of symptoms over time. The case highlights multiple dimensions of chronic SJS, including persistent ocular complications, haematological abnormalities, hepatic enzyme elevations, failed surgical interventions, and the complexities of long-term pharmacological management. By documenting and analysing this case in the context of current evidence, this report aims to contribute meaningfully to the clinical understanding of chronic SJS and to advocate for improved long-term follow-up protocols for SJS survivors.

II. NEED FOR THE STUDY

While the acute presentation of Stevens–Johnson Syndrome is well described in the literature, the chronic, refractory phase of the disease remains comparatively under-reported. Most published series concentrate on acute-phase diagnosis, causative drugs, and short-term mortality, leaving a notable gap in the documentation of long-term, multi-system sequelae that persist and progress over years. There is therefore a pressing need for detailed longitudinal case documentation that captures the evolving ocular, dermatological, haematological, and hepatological burden borne by SJS survivors.

This case is of particular value because it traces a single patient's course over fifteen years following a lamotrigine overdose, encompassing failed corneal surgery, failed skin grafting, progressive visual deterioration, and the haematological and hepatic consequences of long-term immunosuppressive therapy. Such a comprehensive, real-world trajectory is rarely reported, yet it offers important insights into the limitations of current therapeutic paradigms and the complications of chronic methotrexate use in this setting.

By presenting and analysing this case against contemporary evidence, the study aims to reinforce the importance of cautious anticonvulsant prescribing and pharmacogenomic awareness, to highlight the necessity of structured, multidisciplinary long-term follow-up for SJS survivors, and to stimulate further research into therapies for chronic, treatment-resistant disease. The case thereby addresses a clear clinical and academic need to better understand and manage the long-term consequences of drug-induced SJS.

III. CASE PRESENTATION

3.1 Patient Demographics and Background

The patient is a 35-year-old female who first developed features consistent with Stevens–Johnson Syndrome fifteen years ago, placing the onset of disease in her early twenties. The precipitating event was identified as an overdose of lamotrigine, commercially available under the trade name 'Marigold' tablet, which was being prescribed for a neurological or psychiatric indication. The exact indication for lamotrigine at the time of the initial event has not been documented in available records, but the overdose, whether accidental or intentional, resulted in plasma levels sufficient to trigger a severe immune-mediated hypersensitivity reaction [8].

Since the initial acute episode, the patient has experienced a prolonged, non-resolving clinical course with intermittent flares and progressive worsening of both cutaneous and extracutaneous features. She currently presents with a constellation of symptoms involving the ocular, dermatological, haematological, and hepatological systems. Her overall functional status has been significantly compromised, and she has required ongoing medical supervision and pharmacological management.

3.2 Chief Complaints

The patient's primary complaints at the time of the current assessment include bilateral ocular irritation and discomfort, blurring of vision in both eyes, dryness of the oral mucosa (dry mouth), and generalised fatigue likely attributable to her haematological status. She additionally reports persistent difficulty with daily activities due to visual impairment resulting from prior corneal damage and a failed left eye corneal surgery.

3.3 Ocular Findings

Bilateral ocular involvement is one of the most clinically prominent features of this patient's presentation. Examination of both eyes reveals small papular lesions on the conjunctival surface, consistent with conjunctival scarring and papillary hypertrophy commonly observed in chronic SJS-related ocular disease [3]. The patient experiences persistent irritation in both eyes, and she reports blurring of vision that has worsened progressively over the years. Ophthalmic review has been conducted, confirming ongoing ocular pathology.

The pathogenesis of ocular complications in SJS is closely linked to the initial mucosal damage sustained during the acute phase. The conjunctival and corneal epithelium is directly targeted by the cytotoxic T-cell mediated immune response that defines SJS, leading to conjunctival erosion, inflammation, and subsequent fibrosis [2]. Chronic inflammation perpetuates limbal stem cell destruction, which is responsible for corneal epithelial regeneration. The loss of limbal stem cell function results in conjunctivalisation of the cornea, vascularisation, and ultimately, irreversible visual impairment [1].

In this patient, a left eye corneal surgery was previously attempted to restore visual function, likely in the form of corneal transplantation or limbal stem cell transplantation. However, this surgical intervention failed, representing a recognised complication in SJS patients where the chronic inflammatory milieu of the ocular surface prevents successful graft integration and survival [5]. The management of chronic SJS-related ocular disease requires a multidisciplinary approach involving dermatologists, ophthalmologists, and immunologists, given the systemic nature of the underlying pathology. Therapeutic eye drops have been prescribed to manage surface dryness, inflammation, and to prevent further corneal deterioration.

3.4 Dermatological History

The patient's dermatological history is defined by the original acute SJS episode triggered by the lamotrigine overdose, followed by a chronic phase characterised by persistent skin vulnerability and recurrent complications. During the acute phase fifteen years ago, the patient would have presented with the hallmark features of SJS: rapidly spreading erythematous or purpuric macules progressing to blistering and skin detachment [1]. These features are typically accompanied by painful mucous membrane erosions affecting the oral cavity, eyes, and genitalia.

Skin grafting was attempted as a therapeutic intervention to cover areas of denuded skin, but this procedure was unsuccessful. Skin grafting in SJS/TEN is a technically challenging procedure due to the extent of skin loss, the systemic inflammatory state, and the risk of graft rejection in an already compromised immune environment [9]. Failure of skin grafting is associated with prolonged healing times, increased risk of secondary infection, and long-term scarring. The failed grafting procedure in this patient has likely contributed to the persistence of skin abnormalities and functional impairment.

Current skin findings include the sequelae of both the original SJS episode and the failed grafting, with areas of post-inflammatory hyperpigmentation, scarring, and skin fragility. The patient continues to be monitored for any new mucocutaneous manifestations that could signal disease reactivation or progression. Topical oral gel has been prescribed to manage persistent oral mucosal involvement and to alleviate the symptom of dry mouth, which significantly impacts the patient's quality of life.

3.5 Laboratory Investigations

A comprehensive panel of laboratory investigations was conducted as part of the current clinical assessment. The findings are summarised below:

Complete Blood Count (CBC): The patient's haemoglobin level was measured at 10.1 g/dL, consistent with mild to moderate anaemia. This degree of anaemia in a patient receiving methotrexate (Folitrax) may reflect the anti-folate effects of the drug, compounded by the chronic inflammatory state associated with SJS. Neutrophil count was noted at 40% of the total white cell count, representing a relative neutropenia [5]. Chronic methotrexate therapy is a well-recognised cause of myelosuppression, including neutropenia, which underscores the importance of regular haematological monitoring in patients receiving this medication. All other CBC parameters were reported as within normal limits.

Liver Function Tests: Serum SGPT (Alanine Aminotransferase, ALT) was elevated above normal reference ranges. Elevated SGPT is a marker of hepatocellular damage or stress and may reflect either drug-induced hepatotoxicity—particularly relevant in the context of methotrexate therapy, which is known to carry hepatotoxic potential—or systemic

inflammation as part of the ongoing SJS disease process [6]. Alkaline Reserve (AZR) was also elevated, which may indicate metabolic alkalosis or disruption of acid-base homeostasis, a finding that warrants further investigation and clinical correlation. Regular liver function monitoring is essential for patients on long-term methotrexate therapy to detect early signs of hepatic fibrosis or cirrhosis.

Random Blood Sugar (RBS): The patient's random blood glucose was measured at 89 mg/dL, which falls within the normal range and does not suggest active diabetes mellitus or impaired glucose tolerance at this time. This is a relevant baseline measurement given the metabolic stresses associated with chronic disease and immunosuppressive therapy.

Table 1. Summary of Laboratory Investigations

Investigation	Result	Reference Range	Interpretation
Haemoglobin	10.1 g/dL	12–16 g/dL (female)	Mild to moderate anaemia
Neutrophils	40%	40–75%	Relative neutropenia (lower limit)
SGPT (ALT)	Elevated	7–56 U/L	Hepatocellular stress / drug effect
Alkaline Reserve (AZR)	Elevated	Within normal limits	Possible metabolic alkalosis
Random Blood Sugar	89 mg/dL	70–140 mg/dL	Normal

3.6 Current Medications

The patient's current pharmacological regimen includes the following:

1. Folitrax 20 mg Tablet (Methotrexate): Methotrexate is a folate antagonist with well-established immunosuppressive and anti-inflammatory properties. It inhibits dihydrofolate reductase, thereby suppressing purine synthesis and lymphocyte proliferation. In the context of SJS and its sequelae, methotrexate is prescribed to modulate the chronic immune-mediated inflammatory response [10]. The dose of 20 mg per week (or as prescribed) is within the range commonly used for inflammatory dermatological conditions. Potential adverse effects include myelosuppression, hepatotoxicity, mucositis, and pulmonary toxicity, all of which necessitate regular monitoring.

2. Folvite 5 mg Tablet (Folic Acid): Folic acid supplementation is prescribed concurrently with methotrexate to reduce the risk of folate-deficiency-related side effects, including megaloblastic anaemia, mucositis, and hepatotoxicity [5]. The haematological finding of low haemoglobin in this patient may partially reflect folate depletion secondary to methotrexate therapy, despite supplementation. Adequate folate support is essential for maintaining haematological stability.

3. Oral Gel (Topical): A topical oral gel has been prescribed for the management of dry mouth (xerostomia) and oral mucosal lesions, which are persistent sequelae of SJS involving the oral mucosa. These topical preparations typically contain agents that provide lubrication, promote mucosal healing, and reduce pain associated with mucosal erosions.

4. Therapeutic Eye Drops: Ophthalmic preparations have been prescribed to manage chronic ocular surface disease, addressing dryness, inflammation, and irritation of the conjunctival and corneal surfaces. These may include lubricating drops, anti-inflammatory preparations, or antibiotic drops depending on the specific ocular findings.

3.7 Surgical History

The patient has undergone two significant surgical procedures with unsuccessful outcomes. The first was a skin grafting procedure intended to resurface areas of skin loss resulting from the initial SJS episode. This procedure failed, likely due to inadequate graft vascularisation, infection, or immunological rejection in the context of ongoing systemic inflammation [9]. The second was a corneal surgery on the left eye, which was performed to address progressive corneal disease resulting from SJS-associated limbal stem cell deficiency and corneal scarring. This surgical intervention also failed, which is consistent with reported outcomes in SJS patients where the hostile ocular surface environment militates against successful surgical rehabilitation [3].

The cumulative impact of these failed procedures is substantial. The patient is now left with visual impairment in the left eye and continued cutaneous vulnerability. These outcomes underscore the critical importance of preventative

strategies and early aggressive management during the acute phase of SJS, in order to minimise the severity of long-term sequelae [4].

3.8 Disease Timeline Summary

The disease chronology is as follows: approximately fifteen years ago, the patient experienced the acute onset of SJS following an overdose of the lamotrigine-containing 'Marigold' tablet. This acute phase was characterised by the full clinical spectrum of SJS, including cutaneous blistering, mucosal erosions, and systemic symptoms. Over the subsequent years, the patient transitioned into a chronic phase of disease, during which she experienced progressive ocular deterioration, failed skin grafting, failed corneal surgery, and the development of the current symptom complex. The worsening of symptoms over time suggests ongoing immune dysregulation and potentially continued exposure to triggers, compounded by the permanent structural damage sustained during the acute episode.

IV. DISCUSSION

4.1 Aetiology and Drug Implicated

Stevens–Johnson Syndrome is overwhelmingly drug-induced, with medications accounting for approximately 70–80% of all identified cases [8]. Among the vast pharmacological landscape of causative agents, anticonvulsant drugs occupy a central and particularly dangerous position. Lamotrigine, an anticonvulsant sodium channel blocker, has been consistently identified across international pharmacovigilance databases and clinical series as one of the leading precipitants of SJS and TEN [7]. Its mechanism of action involves stabilisation of neuronal membranes and inhibition of glutamate release, but its adverse drug reaction profile includes the capacity to act as a hapten, binding to endogenous proteins and triggering aberrant CD8+ T-cell activation in susceptible individuals [2].

Lamotrigine-induced SJS follows a dose-dependent pattern, with the risk of severe cutaneous adverse reactions markedly increased when the drug is introduced rapidly, titrated aggressively, or when supratherapeutic plasma concentrations are achieved through intentional or accidental overdose [1]. In the present case, the SJS was directly attributed to an overdose of lamotrigine supplied under the brand name 'Marigold' tablet. The pharmacological stress imposed by supratherapeutic lamotrigine levels on the immune system likely provided the antigenic stimulus necessary to precipitate the fulminant hypersensitivity cascade. The prescribing and dispensing of anticonvulsants with narrow therapeutic windows demands rigorous patient education, therapeutic drug monitoring, and careful dose titration protocols to prevent such catastrophic outcomes [11].

It is also notable that pharmacogenomic factors play a significant role in determining individual susceptibility to lamotrigine-induced SJS. Specific HLA alleles, including HLA-B*15:01, have been associated with increased risk of lamotrigine-induced severe cutaneous adverse reactions in certain ethnic populations [6]. Pharmacogenomic screening before initiating lamotrigine therapy in high-risk populations represents a potentially valuable preventive strategy, though its routine implementation remains limited by cost and availability considerations. The integration of such screening protocols into clinical practice could significantly reduce the incidence of drug-induced SJS.

4.2 Pathophysiology

The pathophysiological mechanisms underlying SJS/TEN have been substantially elucidated over the past two decades. The condition represents a paradigmatic example of drug-induced delayed-type hypersensitivity, characterised by the activation and expansion of drug-specific CD8+ cytotoxic T lymphocytes that recognise drug antigens presented on MHC class I molecules expressed by keratinocytes [2]. Once activated, these cytotoxic T cells deploy multiple effector mechanisms to induce keratinocyte apoptosis, including the release of perforin and granzymes, the engagement of Fas ligand (FasL) on the surface of keratinocytes, and the secretion of pro-apoptotic cytokines [6].

Granulysin, a cytotoxic protein released from the granules of CD8+ T cells and NK cells, has been identified as a critical mediator of the widespread keratinocyte apoptosis that characterises TEN and severe SJS. Serum granulysin levels have been shown to correlate with disease severity and have been proposed as a potential biomarker for early diagnosis and prognostication in SJS/TEN [2]. Additionally, elevated serum levels of tumour necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), and interleukin-18 (IL-18) have been documented in acute SJS/TEN, reflecting the intense systemic inflammatory response that accompanies keratinocyte destruction [4].

In chronic cases such as the one presented here, the pathophysiology shifts from acute cytotoxic T-cell-mediated keratinocyte apoptosis to a sustained inflammatory state driven by persistent immune dysregulation. Chronic SJS may be maintained by ongoing antigen-specific T-cell activity, regulatory T-cell dysfunction, and structural disruption of

barrier tissues including the ocular surface and skin [3]. The persistence of inflammatory mediators in the ocular milieu perpetuates conjunctival scarring, corneal neovascularisation, and limbal stem cell exhaustion, leading to the progressive visual impairment observed in this patient over fifteen years of disease.

The hepatological findings in the present case, specifically the elevated SGPT, may reflect multiple overlapping mechanisms. Methotrexate-induced hepatotoxicity is well documented and involves inhibition of folate metabolism in hepatocytes, leading to steatosis and fibrosis with chronic use [5]. Simultaneously, the systemic inflammation intrinsic to chronic SJS may contribute to hepatocellular stress through the direct action of pro-inflammatory cytokines on hepatic tissue. Differentiating between drug-induced and disease-induced hepatic enzyme elevation requires careful clinical correlation and, in some cases, liver biopsy. The elevated AZR may reflect acid-base disturbances secondary to nutritional compromise, respiratory compensation, or medication effects.

4.3 Diagnostic Considerations

The diagnosis of SJS is fundamentally clinical, supported by characteristic histopathological findings on skin biopsy. The diagnostic criteria for SJS require the presence of skin detachment involving less than 10% TBSA, accompanied by mucous membrane involvement in at least two distinct sites and a consistent drug exposure history [1]. Histopathology typically demonstrates epidermal necrosis with full-thickness detachment at the dermo-epidermal junction, lymphocytic infiltration, and satellite cell necrosis (dyskeratosis), reflecting the cytotoxic immunological mechanism [2].

In the chronic phase of SJS, the diagnostic picture is more complex. The florid blistering and epidermal detachment of the acute phase give way to persistent mucosal scarring, ocular sequelae, and post-inflammatory skin changes. The Severity of Illness Score for Toxic Epidermal Necrolysis (SCORTEN) score, which incorporates variables including age, malignancy, heart rate, body surface area involvement, serum urea, glucose, and bicarbonate levels, was originally designed for acute TEN prognostication [4]. Its application in chronic SJS is limited, though individual parameters such as haemoglobin and albumin levels remain relevant markers of disease burden and nutritional status [9].

The haematological findings in this patient—specifically a haemoglobin of 10.1 g/dL and a neutrophil percentage of 40%—reflect the compounded haematological impact of chronic disease and methotrexate therapy. Anaemia in chronic inflammatory conditions results from a combination of iron sequestration, impaired erythropoiesis, and cytokine-mediated red cell destruction. Methotrexate-induced myelosuppression adds a pharmacological dimension to these haematological disturbances [5]. Monitoring of CBC at regular intervals is therefore imperative in this patient.

The small papular lesions observed on the conjunctival surface represent conjunctival papillary or follicular reactions consistent with chronic cicatrising conjunctivitis, a well-recognised sequela of SJS [3]. Progressive cicatricial disease leads to entropion, trichiasis, corneal abrasion, and ultimately, corneal opacification. The failed corneal surgery in the left eye is consistent with the hostile ocular surface environment that exists in chronic SJS, where limbal stem cell deficiency prevents re-epithelialisation of transplanted corneal tissue.

4.4 Management Overview

The management of SJS is stratified according to disease phase: acute, subacute, and chronic. In the acute phase, the primary objectives are the cessation of the causative drug, supportive care analogous to that provided in burn units, wound care, nutritional support, and prevention of secondary infection [1]. The role of specific pharmacological interventions in the acute phase—including systemic corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine, and TNF-alpha inhibitors—remains an area of active investigation, with no single agent demonstrating definitive superiority across all populations [10].

In the current case, the patient has been managed in the chronic phase with methotrexate (Folitrax 20 mg) and folic acid supplementation (Folvite 5 mg). Methotrexate is a folate antagonist that exerts its immunosuppressive effects by inhibiting dihydrofolate reductase (DHFR), an enzyme essential for purine and pyrimidine biosynthesis. By suppressing lymphocyte proliferation, methotrexate reduces the chronic T-cell-mediated inflammation that perpetuates tissue damage in SJS sequelae [6]. Its use in chronic SJS management, while not formally indicated in standard protocols, is supported by its established role in other chronic inflammatory dermatoses and by case series demonstrating benefit in refractory SJS.

Folic acid supplementation alongside methotrexate serves the dual purpose of preventing folate deficiency and mitigating drug-related toxicities including mucositis, cytopenias, and hepatotoxicity [5]. In the present patient, the finding of low haemoglobin (10.1 g/dL) may partially reflect folate depletion or broader myelosuppression despite

supplementation, and dose adjustment or supplementation protocol review may be warranted. The concurrent elevation of SGPT raises concern for methotrexate-induced hepatic injury, necessitating close hepatological surveillance and consideration of dose modification.

Cyclosporin A has emerged as one of the most promising agents for acute SJS/TEN management in recent literature, with evidence suggesting that it may reduce keratinocyte apoptosis by inhibiting calcineurin-mediated cytokine production and cytotoxic T-cell activation [10]. Several retrospective studies and prospective case series have reported improved survival and reduced disease progression with cyclosporin compared to supportive care alone. For chronic SJS sequelae, the management becomes increasingly subspecialty-driven, with ophthalmologists, oral medicine specialists, and wound care experts contributing to a multidisciplinary plan.

Recent advances in the understanding of SJS pathophysiology have opened new therapeutic avenues. Biologic agents targeting specific inflammatory mediators—including etanercept (anti-TNF-alpha), omalizumab (anti-IgE), and dupilumab (anti-IL-4/IL-13)—have been explored in refractory or chronic SJS/TEN [10]. Additionally, the use of amniotic membrane transplantation in the management of SJS-related ocular surface disease has gained traction as a strategy to reduce scarring and promote corneal re-epithelialisation [3]. For the current patient, whose left corneal surgery has failed, consideration of amniotic membrane transplantation or alternative limbal stem cell rehabilitation strategies may represent viable options in the future management plan.

4.5 Ocular Complications in Depth

Ocular involvement in SJS is among the most clinically significant and functionally debilitating aspects of the disease. Approximately 50–88% of SJS patients develop some degree of ocular involvement during the acute phase, and a substantial proportion progress to chronic ocular surface disease [3]. The inflammatory cascade initiated by drug-specific cytotoxic T cells in the conjunctival epithelium leads to conjunctival erosion, goblet cell loss, subepithelial fibrosis, and destruction of the limbal stem cell niche [2].

Goblet cell loss is particularly significant because these specialised epithelial cells are responsible for producing mucin, a critical component of the tear film that maintains ocular surface hydration and stability. Loss of goblet cells leads to tear film instability, chronic dry eye syndrome, and repeated epithelial microtrauma [1]. The resultant chronic exposure keratopathy, combined with the loss of regenerative limbal stem cells, creates a self-perpetuating cycle of corneal damage that is extremely difficult to interrupt without surgical intervention.

In the present patient, the papular lesions observed on the conjunctival surface likely represent areas of papillary hypertrophy and conjunctival scarring consistent with cicatricial conjunctivitis. This chronic cicatricial process can lead to the development of symblephara (adhesions between the bulbar and palpebral conjunctiva), entropion (inward turning of the eyelid), and trichiasis (misdirected eyelashes abrading the corneal surface) [3]. Each of these complications compounds the degree of corneal injury and visual impairment. The blurring of vision reported bilaterally in this patient is consistent with the combination of corneal opacification, tear film instability, and possible lens changes secondary to chronic inflammation.

The management of chronic SJS-related ocular disease is multifaceted and demands close ophthalmological supervision. Therapeutic strategies include intensive lubricant therapy using preservative-free artificial tears, anti-inflammatory eye drops (topical corticosteroids or cyclosporin ophthalmic emulsion), autologous serum eye drops, bandage contact lenses to protect the corneal surface, and surgical interventions such as amniotic membrane transplantation, mucous membrane grafting, and keratoprosthesis implantation for end-stage corneal disease [4]. The failure of left corneal surgery in this patient emphasises the need to optimise the ocular surface environment before any future surgical attempt, potentially through systemic immunosuppression and intensive topical management.

4.6 Haematological Considerations

The haematological abnormalities identified in the present case merit detailed discussion, as they represent both complications of the underlying disease and potential adverse effects of the therapeutic regimen. The patient's haemoglobin level of 10.1 g/dL (below the normal female reference range of 12–16 g/dL) indicates mild to moderate anaemia, which may have several contributory mechanisms in this clinical context.

Firstly, anaemia of chronic disease (ACD), also termed anaemia of inflammation, is a common comorbidity in patients with chronic inflammatory conditions. The inflammatory milieu associated with ongoing SJS activity stimulates the production of hepcidin, a hepatic acute-phase protein that reduces intestinal iron absorption and sequesters iron within

macrophages, thereby limiting the availability of iron for erythropoiesis [5]. Elevated levels of pro-inflammatory cytokines, particularly TNF-alpha and IL-6, also directly suppress erythropoietin production and impair the bone marrow's response to erythropoietic stimuli.

Secondly, methotrexate-induced suppression of folate metabolism can lead to megaloblastic anaemia, characterised by the production of enlarged, dysfunctional red blood cells due to impaired DNA synthesis [6]. While folic acid supplementation with Folvite 5 mg is intended to counteract this effect, it may not be fully protective in all patients, particularly at higher methotrexate doses or in patients with pre-existing folate deficiency or malnutrition.

The relative neutropenia, with neutrophils comprising only 40% of the total white cell count, may similarly reflect methotrexate-induced myelosuppression or the influence of chronic inflammatory cytokines on granulopoiesis [5]. Neutropenia increases the patient's susceptibility to bacterial infections, which is of particular relevance given the ongoing skin and mucosal barrier compromise associated with chronic SJS. Monitoring of absolute neutrophil count (ANC) and appropriate management of any significant neutropenia are essential components of this patient's ongoing care.

4.7 Hepatological Findings

The elevation of SGPT (ALT) in this patient requires careful clinical interpretation. ALT is an enzyme predominantly localised to hepatocytes, and its elevation in the serum is a sensitive marker of hepatocellular damage or increased hepatocyte membrane permeability. In the context of long-term methotrexate therapy, elevated ALT is a recognised finding that may indicate hepatic inflammation, steatosis, or early fibrosis [6].

Methotrexate-induced hepatotoxicity is cumulative and dose-dependent, with the risk of significant liver damage increasing with total cumulative dose, duration of therapy, and the presence of risk factors such as alcohol consumption, obesity, diabetes mellitus, and pre-existing liver disease. Regular monitoring of liver enzymes is therefore mandatory, and the threshold for liver biopsy should be considered when ALT persistently exceeds twice the upper limit of normal [5]. In cases of confirmed significant hepatic fibrosis or cirrhosis, methotrexate should be discontinued and alternative immunosuppressive strategies pursued.

The elevated AZR (Alkaline Reserve) in this patient may reflect an acid-base disturbance. Metabolic alkalosis can result from several conditions including persistent vomiting (relevant in patients with severe oral mucositis), hypochloraemia, or medication effects. In the context of SJS, persistent mucosal disease and impaired oral intake can lead to nutritional deficits and electrolyte imbalances that manifest as acid-base disturbances [9]. The elevation of AZR warrants further electrolyte analysis, blood gas assessment, and nutritional evaluation.

4.8 Quality of Life and Psychosocial Impact

The impact of chronic SJS on quality of life is profound and multidimensional. Patients with persistent ocular disease, oral mucosal involvement, and skin changes experience significant impairments in daily functioning, social interaction, psychological wellbeing, and occupational capacity [7]. The present patient has been living with this condition for fifteen years, and the progressive nature of her disease trajectory—characterised by failed surgical interventions and worsening symptoms—likely carries a considerable psychological burden.

Studies examining health-related quality of life (HRQoL) in SJS survivors consistently demonstrate elevated rates of depression, anxiety, post-traumatic stress disorder, and social isolation [4]. Dry mouth, a symptom reported by this patient, is particularly impactful as it affects eating, speaking, oral hygiene, and social confidence. Bilateral visual impairment adds a further dimension to functional disability, potentially affecting independence, employment, and self-care capacity. Comprehensive psychosocial assessment and referral to mental health support services should be integral components of the long-term management plan for this patient.

Multidisciplinary team involvement is crucial for optimising outcomes in chronic SJS. The care team for this patient ideally includes a dermatologist for skin and mucosal management, an ophthalmologist for ocular disease monitoring and intervention, a haematologist for management of anaemia and neutropenia, a hepatologist for monitoring of liver function, a nutritionist for addressing nutritional deficits, and a psychologist or psychiatrist for psychosocial support [10]. Coordination among these specialties, with a clear communication framework and regular multidisciplinary reviews, represents best practice for complex chronic SJS cases.

4.9 Long-Term Prognosis and Follow-Up

The prognosis for patients with chronic SJS complicated by bilateral ocular disease, failed surgical interventions, and ongoing systemic manifestations is guarded. Whilst SJS itself is not invariably fatal in the chronic phase, the cumulative morbidity of progressive visual impairment, mucosal dysfunction, haematological compromise, and medication toxicities substantially diminishes overall wellbeing and functional capacity [8].

The long-term follow-up of SJS survivors should include regular dermatological reviews, ophthalmic assessments, haematological monitoring (CBC at least quarterly while on methotrexate), liver function testing (LFTs every 4–8 weeks), and assessment of quality of life outcomes. Any new drug prescriptions must be reviewed meticulously for potential cross-reactivity or re-triggering risk [11]. Pharmacovigilance and patient education about the risks of specific medications, particularly anticonvulsants and sulfonamides, are essential preventive measures in this patient's ongoing management.

In terms of future therapeutic options for this patient, the failure of conventional surgical approaches for ocular rehabilitation and skin grafting raises the question of emerging therapies. Keratoprosthesis (artificial cornea) implantation may be considered as a last resort for the left eye, with Boston KPro being among the most studied devices in SJS-related end-stage corneal disease [3]. Systemic biologic therapies targeting key inflammatory mediators may also be considered if the disease remains active and unresponsive to current immunosuppressive therapy. The evolving landscape of SJS/TEN management offers cautious optimism for patients with refractory disease.

V. CONCLUSION

This case report presents a clinically significant and instructive account of a 35-year-old female patient with a fifteen-year history of chronic, progressive Stevens–Johnson Syndrome secondary to an overdose of lamotrigine (Marigold tablet). The case highlights the devastating long-term consequences of drug-induced SJS, including bilateral ocular involvement with failed corneal surgery, failed skin grafting, persistent oral mucosal disease, haematological abnormalities, and hepatological changes secondary to chronic pharmacological management. The patient's ongoing dependence on methotrexate (Folitrax) and folic acid supplementation (Folvite), together with topical ocular and oral preparations, reflects the complexity of managing a disease that, despite originating as an acute drug reaction, has evolved into a chronic, multi-system condition demanding sustained multidisciplinary care.

Several key lessons emerge from this case. First, the prevention of drug-induced SJS through careful drug selection, appropriate dosing, pharmacogenomic screening where available, and patient education represents the most effective strategy for avoiding the catastrophic long-term burden documented in this patient. Second, once SJS has occurred, the aggressive management of the acute phase—including rapid withdrawal of the causative drug and prompt initiation of appropriate immunosuppressive therapy—is critical to limiting the extent of tissue damage and the severity of long-term sequelae. Third, the chronic management of SJS survivors requires ongoing, proactive, multidisciplinary oversight that addresses not only the cutaneous and mucosal manifestations of the disease but also its ocular, haematological, hepatological, and psychosocial dimensions.

The ocular complications encountered in this patient, characterised by small conjunctival papular lesions, bilateral blurring of vision, and failure of corneal surgery, exemplify the challenges posed by SJS-associated limbal stem cell deficiency and chronic ocular surface inflammation. Future therapeutic strategies, including amniotic membrane transplantation, keratoprosthesis implantation, and targeted biologic therapies, may offer improved outcomes for patients in whom conventional management has been unsuccessful.

The haematological and hepatological findings in this patient serve as a reminder of the need for vigilant monitoring of treatment-related toxicities in patients receiving long-term immunosuppressive therapy. Regular CBC, liver function testing, and metabolic assessments are non-negotiable components of the monitoring protocol for patients managed with methotrexate.

This case contributes to the limited but growing literature on chronic, refractory SJS and underscores the need for dedicated long-term follow-up clinics for SJS survivors. The progressive nature of this patient's disease trajectory over fifteen years, despite ongoing medical management, highlights the gaps that exist in current therapeutic paradigms for this condition. Future research should focus on elucidating the mechanisms that sustain chronic immune dysregulation

in SJS survivors, identifying novel therapeutic targets, and developing evidence-based protocols for the long-term care of this vulnerable patient population.

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REFERENCES

[1] Frantz R, Huang S, Are A, Motaparthi K. Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: A Review of Diagnosis and Management. Medicina [Internet]. 2021 Aug 28;57(9):895. Available from: https://doi.org/10.3390/medicina57090895

[2] Hama N, Aoki S, Chen CB, Hasegawa A, Ogawa Y, Vocanson M, et al. Recent progress in Stevens–Johnson syndrome/toxic epidermal necrolysis: diagnostic criteria, pathogenesis and treatment. British Journal of Dermatology [Internet]. 2024 Aug 14;192(1):9–18. Available from: https://doi.org/10.1093/bjd/ljae321

[3] Watanabe Y, Hama N. Recent advances in the diagnosis and treatment of Stevens–Johnson syndrome/toxic epidermal necrolysis. Allergology International [Internet]. 2025 Jun 10;74(3):345–55. Available from: https://doi.org/10.1016/j.alit.2025.05.008

[4] Shah H, Parisi R, Mukherjee E, et al. Update on Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: Diagnosis and Management. Am J Clin Dermatol. 2024;25:891–908. Available from: https://doi.org/10.1007/s40257-024-00889-6

[5] Chang HC, Wang TJ, Lin MH, Chen TJ. A review of the systemic treatment of Stevens–Johnson Syndrome and toxic epidermal necrolysis. Biomedicines [Internet]. 2022 Aug 28;10(9):2105. Available from: https://doi.org/10.3390/biomedicines10092105

[6] Hasegawa A, Abe R. Stevens–Johnson syndrome and toxic epidermal necrolysis: Updates in pathophysiology and management. Chinese Medical Journal. 2024 Oct 5;137(19):2294–307. DOI: 10.1097/CM9.0000000000003250

[7] Bayram-Ozgur D, Colak O, Gultekin O, Akici N, Onal ZE, Akici A. Pediatric Stevens–Johnson syndrome and toxic epidermal necrolysis: age-stratified insights from the FAERS database. Jornal De Pediatria [Internet]. 2025 Oct 23;101(6):101455. Available from: https://doi.org/10.1016/j.jped.2025.101455

[8] Sharma V, Sethuraman G, Minz A. Stevens Johnson syndrome, toxic epidermal necrolysis and SJS-TEN overlap: A retrospective study of causative drugs and clinical outcome. Indian Journal of Dermatology Venereology and Leprology [Internet]. 2008 Jan 1;74(3):238. Available from: https://doi.org/10.4103/0378-6323.41369

[9] Almadfaa AO, Alattas MK, Aleissa AI, Bormah AW, Alqurashi HM, Felemban AAM, et al. An Overview on the Evaluation and Management of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. Int J Pharm Res Allied Sci. 2022;11(1):29–34. Available from: https://doi.org/10.51847/K833tMZjQP

[10] Villarreal JDM, La Garza JAC, Ionescu M, Tatu AL, Busila C, Mokni M, et al. Stevens–Johnson Syndrome and toxic Epidermal necrolysis: A review of current management and Innovative therapies. International Journal of Dermatology [Internet]. 2025 Apr 15;64(7):1164–72. Available from: https://doi.org/10.1111/ijd.17768

[11] Lee E, Knox C, Phillips E. Prevalence of antibiotic-induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN): a systematic review and meta-analysis. Journal of Allergy and Clinical Immunology [Internet]. 2023 Feb 1;151(2):AB57. Available from: https://doi.org/10.1016/j.jaci.2022.12.182