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## Stevens-Johnson syndrome in an 18-year-old Nigerian female: a case report

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### Abstract

**Purpose:** This is a Stevens-Johnson syndrome (SJS) case with an atypical presentation. Stevens-Johnson syndrome is a hypersensitivity reaction distinguished by necrosis of skin tissue and mucosal linings including the genitals and eyes. It usually occurs as a reaction to certain medications. The condition is regarded as a medical emergency and management is tailored according to presenting symptoms with emphasis on airway and hemodynamic stability, lesion treatment, and prevention of opportunistic infection. While the condition is not hereditary, genetic codes passed on may increase the risk of similar immune-mediated hypersensitivity responses among progenies of affected individuals. Cyclosporine and other immunomodulatory therapeutics have shown promise in managing this condition.

**Case Report:** This patient presented with severely reduced vision. The patient also had a recent history of bilateral ocular adnexal surgery and a family (father) history of kidney disease. An extensive case history, ocular workup, and microbial sensitivity testing were carried out to reach a diagnosis. The patient was initially placed doxycycline, Vitamin C, Moxifloxacin and Fluconazole. These were later adjusted when culture results returned. Unfortunately, due to the delay in presentation, the condition had progressed significantly, and management was palliative rather than restorative.

**Conclusion:** A knowledge of SJS and quick intervention is key to minimizing morbidity and possible mortality from this condition. Management of this condition is multi-disciplinary and eye care providers should examine sufferers for ocular involvement so as to mitigate visual morbidity.

**Key words:** Steven-Johnson's Syndrome, Atypical, Necrosis, Cyclosporins, Microbial Sensitivity testing

### Introduction

Stevens-Johnson syndrome (SJS) is a type IV hypersensitivity antigenic response. It has largely been reported to begin with an upper respiratory tract infection<sup>1,2</sup>. This usually is part of a 1 to 14-

day prodrome during which fever, sore throat, chills, headache, and malaise may be present. Vomiting and diarrhea are occasionally noted as part of the prodrome. Common ocular symptoms include tearing, pain sensation, blepharospasm,

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itching, grittiness, heavy lids, foreign body sensation, decreased vision, burning sensation, and photophobia.

In most cases, mucocutaneous lesions develop abruptly. Clusters of outbreaks last from 2-4 weeks. The lesions are typically non-pruritic. A history of fever or localized worsening should suggest a superimposed infection; however, fever has been reported to occur in up to 85% of cases<sup>3</sup>. The involvement of oral and/or mucous membranes may be severe enough that patients may be unable to eat or drink. Patients with genitourinary involvement may complain of dysuria or an inability to void due to obstructive uropathy and acute kidney injury early on in the disease<sup>4</sup>.

A history of a previous outbreak of Stevens-Johnson syndrome or of erythema multiforme may be elicited. Recurrences may occur if the responsible agent is not eliminated or if the patient is re-exposed. Patients may complain of a burning rash that begins symmetrically on the face and the upper part of the torso. This may be accompanied by ocular symptoms. In addition to characteristic dermal involvement, lesions in SJS may involve the oral mucosa (with evidence of lingual desquamation and labial shedding), esophagus, pharynx, larynx, vagina & urethra. Delineation of a drug exposure timeline is essential, especially in the one to three weeks preceding the cutaneous eruption.

## Case Report

An 18-year-old African female, presented on

the 31st of August, 2023 with specific ocular complaints of poor vision associated with occasional headaches, pain and burning sensation in both eyes which started six months ago. The patient reported initially experiencing headache symptoms and a fever prior to the onset of her chronic illness more than four months prior to presentation. She had self-medicated on oral anti-malarials (artesunate/amodiaquine) at the time. Patients' blood pressure and random blood sugar were unremarkable.

Patient's mother hinted at observing a few blisters around her lips initially before she (the patient) developed what was presumed chicken pox. According to their reports, the patient subsequently developed extensive skin lesions with concurrent progressive ocular discomfort. Local concoctions were applied to both eyes by a 'traditional' healer about 2 months before this visit to the clinic. Patient then visited a hospital to complain of deteriorating vision and difficulty opening both eyes for which she underwent bilateral surgery for the lysing of adherent membranes which reportedly inhibited voluntary lid elevation. The patient then reportedly opened her eyes voluntarily only after said 'surgical' intervention was done. She had instilled some eyedrops including Betamethasone/Neomycin sulfate (Bet-N), and Tobramycin/Dexamethasone phosphate (Tobrex) drops lasting less than one month before presentation; as well as Ciprofloxacin eyedrops at the early stages of this condition. Her mother then reported that only Diclofenac and Atropine eyedrops were still being instilled

3. Paulmann M, Mockenhaupt M. Fever in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Pediatric Cases: Laboratory Work-up and Antibiotic Therapy. *Pediatric Infectious Diseases Journal*. 2017;36(5):513-5. <https://doi.org/10.1097/inf.0000000000001571>

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into both eyes at the presentation. The patient's last oculo-visual examination was two weeks earlier at that same facility.

The patient's family ocular history was unremarkable. The patients' family medical history revealed that her father had recently been diagnosed with kidney disease following a bout of presumed malaria fever for which he took the same anti-malarial medication. Further questioning revealed her father regularly used artesunate/amodiaquine to manage malaria in the past. Family history was unremarkable for an occurrence of generalized cutaneous eruptions.

Patients' blood pressure and random blood sugar were unremarkable. Physical examination revealed cutaneous presentations (Figure 1) including an even distribution of flat, patchy hyperpigmented scars, most notably along the arms, legs and sides of the neck (Figure 2 and 3), anonychia (loss of fingernail structure on both hands and feet). These multifocal pigmented scars possessed a 'pseudo' bulls-eye morphology. The patient was then sent to a general physician for characterization and confirmation of these lesions.



**Figure 1.** Visible irregularities on the tongue suggestive of previous desquamation



**Figure 2.** Patchy Hyperpigmented scars on the face and neck



**Figure 3.** Patchy Hyperpigmented scars on an upper limb

Patient's entry visual acuity was hand motion (HM) for both eyes. Both lids were mildly oedematous; lashes were matted due to profuse mucopurulent conjunctival discharge with accompanying dry mucoid collections at the medial canthi. There was marked conjunctival hyperemia, chemosis and symblepharon

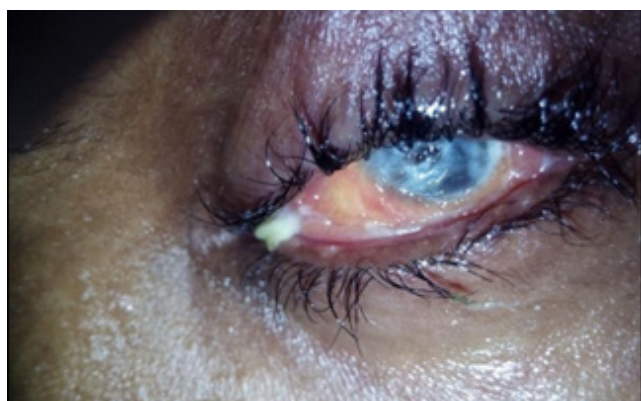
formation at the inferior fornices. There was also diffuse limbal opacification and generalized fluffy corneal epithelial infiltrates; with visible iris prolapse through perforated corneas in both eyes. No corneal staining patterns were observed. The anterior chamber, pupils and posterior segment were impossible to assess clinically (Figures 4 and 5). Patients' responses to cotton fiber contact indicated hypoesthesia.

First impressions following a primary assessment of her ocular signs included:

- Fulminating fungal keratitis
- Severe ocular surface disease
- Ocular cicatricial pemphigoid

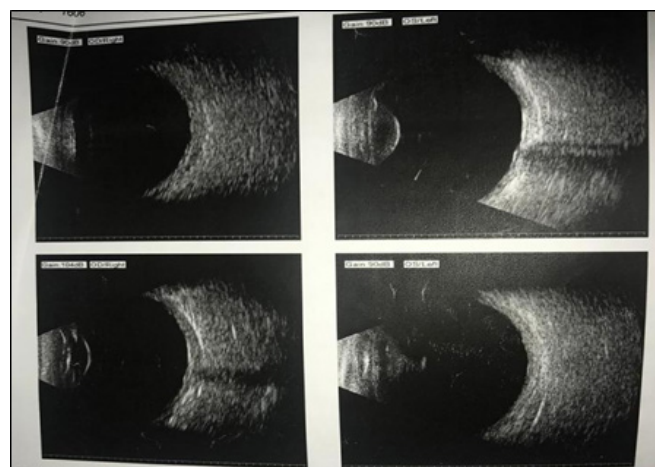


**Fig. 4:** Right eye of patient showing partial symblepharon and mucopurulent discharge.



**Fig. 5:** Left eye of patient showing partial symblepharon and mucopurulent discharge.

Ocular ultra sound scan (B-scan) was performed for both eyes (with copious gel applied to act as a soft pad against the lids). This demonstrated an intact retinal outline, and no gross atypical intraocular reflections indicative of posterior segment pathology. However, multiple aberrations could be observed anterior to- and around the iris-lens interface in both eyes. Hence, a severe, localized anterior segment disease was suggested (Figure 6).



**Fig 6.** Ocular Ultrasound scan of both eyes of case patient.

Swabs of mucopurulent conjunctival discharge were also collected for microbial culture & sensitivity testing. A retroviral screening was ordered to rule out immunocompromise: for which results returned negative. The patient was placed on Doxycycline (100mg b.i.d PO  $\times$  1/52) and Ascorbate tablets (800mg dly  $\times$  1/52). Patient was also placed on Fluconazole & Moxifloxacin eyedrops and was instructed to apply these four times daily.

Patient and her family were counseled on poor prognosis associated with her late presentation. Patient was instructed to return two days later for a follow-up visit.

## Follow Up (2/9/20)

Microbial culture and sensitivity testing of conjunctival discharge samples returned with cultures revealing heavy growth of *Candida* spp., thus all contraindicated medications were discontinued. Visual acuity was HM in both eyes. Mucoid discharge had also greatly resolved. Conjunctival hyperemia, chemosis and symblepharon were still visible. Patient was counseled to visit a corneal surgeon to manage severe unresolved bilateral iris prolapse.

## Discussion

Severe cutaneous eruptive syndrome is usually included amongst the differentials based on the findings of a physical exam. Acute SJS can be clinically differentiated by the appearance of multiple blisters, with a centric zone of oedema; this intra-lesional asymmetry often persists through stages of healing, resulting in 'targetoid' scarring of areas involved. Laboratory workup such as complete: to detect eosinophilia; and viable inflammatory markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are most translational during acute phases of disease. Clinical diagnosis in all settings is aided by the visualization of multiple target-like lesions on the skin; coupled with mucosal involvement (via mucous membrane erosions) most noticeable along ocular surface mucosa, and linings of the mouth.

Thus, following gross physical examination of signs; and a review of the history, an impression of late ocular sequelae resulting from prolonged drug-induced hypersensitivity syndrome (DIHS) was made.

Drug induced hypersensitivity syndrome (DIHS) is a term which refers to rare adverse reactions to certain medications. Symptoms and signs of disease often include acute fever and malaise with subsequent widespread characteristic cutaneous manifestations, with or without lymphedema<sup>5-7</sup>. Emergent treatment is mostly required, as late presentations may become complicated with multi-organ 'autoimmune' disease involving the liver, kidneys, lungs, heart, and ocular surface; often leading to visual impairment<sup>8</sup>. The presentations of drug-induced 'immune-mediated' hypersensitivity syndrome have been widely reported in literature with the spectrum of severity ranging from Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) to acute generalized exanthematous pustulosis (AGEP)<sup>9-10</sup>.

Both AGEP and SJS/TEN are considered severe mucocutaneous reactions. Although their pathogenesis is not completely understood, they are thought to be immune-mediated conditions, generally triggered mostly by medications, and occasionally of underlying infectious etiology<sup>11</sup>. SJS/TEN are regarded as a continuum of diseases whose characteristic sign is keratinocyte necrosis,

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secondary detachment of the epidermis, and mucous membrane involvement. Gross signs of disease usually include erythematous, targetoid, annular macules; flaccid bullae, large painful erosions; with a positive Nikolsky sign (lateral pressure on the skin results in shedding of the epidermis)<sup>12</sup>. SJS usually affects the mucous membranes, but skin detachment is less than 10% of total body surface. TEN involves detachment of more than 30% of body surface area and mucous membrane involvement is the rule. SJS/TEN overlap is defined by skin detachment of 10% to 30% of body surface area. Higher preponderance for disease occurrence has been reported amongst individuals infected with the human immunodeficiency virus (HIV - estimated incidence 1:1000); medications are also reportedly causative in more than 80% of cases presenting with SJS/TEN<sup>13</sup>. In contrast, AGEP is considered a less severe condition, with less mucosal involvement and with a shorter latency and faster resolution after withdrawal of the culprit drug. The disease is characterized by generalized pinhead pustules and spongiform sub-corneal or intra-epidermal pustules. It can present with a positive pseudo-Nikolsky sign resulting from skin detachment consequent to coalescence of pustules<sup>14</sup>. Although treatment of AGEP and SJS/TEN remains a controversial topic, prompt drug withdrawal and supportive care, as well as immunomodulation are the cornerstones of therapy. In some patients, clinical distinction can be

challenging. In acute stages, AGEP can present with atypical target-like lesions and blisters mimicking SJS/TEN. Nevertheless, history, clinical course and histopathologic findings (during the acute phase of disease) are key to correct diagnosis. Patch tests of the suspected drug are more often positive in AGEP patients than in those with SJS/TEN.

Toxic epidermal necrolysis (TEN) is an acute disorder. Its characteristics include generalized erythematous macules, targetoid lesions<sup>15</sup> and full-thickness necrosis involving more than 30% of skin surface. Frequently, the mucous membranes are also affected. Almost all cases of TEN are associated with medication exposure, and the mortality rates have been documented up to 40%<sup>16</sup>.

The clinical presentation of Stevens-Johnson syndrome consists of patches of purplish discolored macules and targetoid lesions, full-thickness necrosis of the outer layer of the skin, although with lesser detachment of the skin's outer surface; and mucous membrane involvement<sup>17</sup>. Just as with toxic outer skin necrolysis, medications are known triggers for this condition. If medications are implicated in causation, symptoms may likely appear within 4-28 days after exposure to the drug(s)<sup>18</sup>. In some cases, infections caused by bacteria (*Mycoplasma*) may induce Stevens-Johnson syndrome or toxic epidermolysis syndrome, particularly in children and young adults<sup>19</sup>; although it may present unusually

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without cutaneous lesions and only involvement of the mucosa. This is known as Fuchs' syndrome. The mortality rate reported for Stevens-Johnson syndrome is much lower than that rate associated with TEN. The numbers approach 5% of cases of SJS compared to >14% of TEN cases<sup>20</sup>.

The outcomes of the disease process, even with management is to a large extent, a function of the extent of skin sloughing. As the degree of skin sloughing increases, the rate of mortality increases<sup>21</sup>. For unclear reasons, however, the disease sequelae in some patients simply stops advancing, and rapid re-epithelialization of affected tissues follows. The mortality rate for patients who have a greater dermatological involvement (including sloughing off of the skin) usually holds a higher mortality rate<sup>22</sup>.

Common "high-risk" inducing medications reported in literature with varying racial predilection include:

Anticonvulsants e.g. lamotrigine

- ▶ Antibiotics e.g. Amoxicillin, ampicillin,
- ▶ azithromycin, vancomycin, levofloxacin, minocycline, rifampicin, streptomycin.

Antineoplastic medications.

- ▶ Anti-retroviral drugs (ARVDs): e.g. Abacir,
- ▶ nevirapine

Acetaminophen;

- ▶ Other NSAIDs e.g. Celecoxib, Aspirin,
- ▶ Piroxicam
- Sulfonamides e.g. dapsone,
- ▶ sulfamethoxazole-trimethoprim, sulfadoxine, sulfasalazine
- Others reported pharmacologic triggers
- ▶ include: Omeprazole, allopurinol<sup>23-24</sup>.

Meanwhile, antipyretic drugs are reported to pose greater risk of triggering SJS/TEN amongst Japanese pediatric population, following repeated usage<sup>25</sup>.

Further discussion of this case is warranted, because of its unusual presentation and attributed cause. First, the clinical onset of the case was reportedly less than a week after drug initiation. The only recognizable trigger was Amodiaquine/Artemether (as it was the only systemic medication reported to be used prior to onset of eruptions, in the patient's clinical history). It's propensity to contribute to hyper-acute immunological disease is not vastly reported in literature, however, use of the antimalarial medication- amodiaquine- which is a frontline therapy for the treatment of uncomplicated malaria has been associated with reports of acute dystonic reaction and bradycardia in young individuals. This follows both inadvertent overdose and standard therapeutic dosage<sup>26</sup>. The

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patient's general external appearance also indicated that the disease process had run a prolonged course; with complete resolution of skin blisters and end-point scarring, although mild to moderate mucous membrane involvement remained (notably within and around the buccal mucosa).

As earlier noted, the ocular presentation suggested that there had been slow resolution and resultant perforation of corneal epithelial/keratolytic defects with secondary fungal infection confirmed by microbial culture and sensitivity testing. Numerous studies report on the predisposition to develop non-healing or very slow-healing ulcerative keratitis among patients who had been afflicted with prolonged clinical course of immune-mediated muco-cutaneous disease, mostly due to complete epidermal sloughing of the ocular surface<sup>27</sup>.

It is also important to exclude potential underlying viral etiologies in contributing to such severe hyper-immune reactions. Corneal disease associated with SJS may mimic herpes zoster keratitis via its prolonged course and poor cicatrization. However, corneal hypoesthesia is often absent<sup>28</sup>.

Amongst patients with Stevens-Johnson syndrome, greater than 30% develop ocular sequelae<sup>29</sup>. Complications resulting from prolonged sequel may include the following:

- Chronic cicatrizing conjunctivitis
- Chronic dry eye disease

- Corneal epithelial defects
- Corneal stromal ulcers
- Corneal perforation
- Endophthalmitis

Keratitis is frequently the first presentation in sequel of disease history; thus, a detailed assessment of the patient's ophthalmic history is critical. Ocular lesions are especially worrisome, because of the associated high risk of cascading into more advanced stages within the known sequelae of the disease. In 20-75% of SJS sufferers, long-standing ocular sequelae can occur and these often cause severe visual impairment<sup>30</sup>. They frequently occur from the action of multiple pathological processes, often culminating in visual impairment and ultimately blindness.

Ophthalmic complications may also include lid deformities like ectropion and entropion. Other anomalies may include trichiasis, distichiasis and dry eye syndrome. Lagophthalmos, corneal erosions, corneal ulcerations, corneal thinning and neovascularization, keratinization, infectious keratitis and chronic photosensitivity have also been reported in literature<sup>31</sup>. Blindness or severe visual impairment may occur as a result of severe keratitis or even panophthalmitis in 3-10% of a patient pool<sup>30</sup>. Stenosis of the Vagina and scarring of the penis have also been reported while complications of the kidneys are rarely reported<sup>32-33</sup>.

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Skin lesions may resolve leaving behind a patchwork of pigmentation (both hyperpigmentation and hypopigmentation). Furthermore, there may be an abnormal regrowth of both fingernails and toenails.

Another essential differential is ocular cicatricial pemphigoid/ocular mucous membrane pemphigoid (OCP/OMMP). This is due to incongruencies between our patient's presentation and OCP pathogenesis. OCP is a chronic disorder characterized by recurrent episodes of bilateral non-infectious conjunctivitis. Extraocular involvement, on the other hand, is mostly restricted to mucosal tissue. Genetic preponderance usually plays a role; same as DIHS. However, immune-sensitizing factors are not fully understood. In our case report, history suggested that the patient's went through extended time period to disease resolution more typical to SJS/TEN. Characteristic annular scarred lesions along the skin also suggest targetoid

morphology of prior active lesions. Characteristic loss of keratin/nail structure also suggests similar disease processes.

History of abuse of most likely plant-based "traditional eye medications" could, to an extent, account for abnormal ocular surface fungal growth. Although topical antibiotic abuse could also be a factor. Nonetheless, besides possible autoimmune corneal melt, unabrupted fungal keratitis could be suggested amongst most likely causes of full thickness corneal perforations upon presentation.

Lastly, in this case; keratoplasty is the most cogent management plan. High index of suspicion for autoimmune disease with atypical microbial growth pose very high-risk outcomes to surgical intervention.

## Conclusion

With proper pharmacovigilance amid an already alarming incidence of self-medication in the Nigerian setting<sup>34</sup>, spates of medication abuse can be reduced. DIHS (the umbrella term describing SJS and other aforementioned related syndrome) is only a single consequence of immune-related incompatibility to known endogenous triggers. In this case, the suggested pharmacologic trigger is particularly bothersome, because numerous medications comprising the aforementioned active ingredients are frequently obtainable over-the-counter without prior drug hypersensitivity ever being elicited. Although several cases of immunologic reactions have been reported amongst African children treated for malaria with similar pharmacologics<sup>35</sup>;

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  35. Adjei GO, Darkwah AK, Goka BQ, Bart-Plange C, Alifrangis ML, Kurtzhals JA, Rodrigues OP. Parents' perceptions, attitudes and acceptability of treatment of childhood malaria with artemisinin combination therapies in Ghana. *Ghana Medical Journal*. 2009; 43(3):99-106. <https://doi.org/10.4314/gmj.v43i3.55324>

no clear 'red-tape' has been drawn on the illicit use of predisposing medications. Thus, besides driving the much-desired progress in areas of pharmacovigilance particularly with regards to drug-toxicity profiles; caregivers and health workers must be continuously re-educated of the telltale signs suggesting acute drug-induced hypersensitivity syndrome (DIHS). Quick realization and quick action would help save lives and limit functional loss as severe as our case of interest, and prevent possible recurrence<sup>36</sup>. In order to achieve this, a strict interdisciplinary approach culminated with rheumatologic consultations; early dermatological and eye care specialists' involvement cannot be overemphasized.

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