Case Report: Severe Eye Complications from Stevens-Johnson Syndrome in a Human Immunodeficiency Virus–Infected Patient in Malawi

Markus Schulze Schwering,* Petros Kayange, Joep J. van Oosterhout, and Martin S. Spitzer

Department of Ophthalmology, and Department of Medicine, College of Medicine, University of Malawi, Blantyre, Malawi; Lions Sight First Eye Hospital, Blantyre, Malawi; University Eye Hospital, Tübingen, Germany

Abstract. Stevens-Johnson syndrome (SJS) is a severe form of erythema multiforme that primarily affects skin and mucous membranes. In Malawi, manifestations of SJS may become more common in human immunodeficiency virus–infected patients receiving nevirapine-based antiretroviral therapy (ART) because the CD4 cell threshold for starting ART has increased from 250 to 350 cells/ μ L. We describe a patient with severe ocular complications from SJS that developed soon after initiation of nevirapine-based ART and cotrimoxazole preventive treatment, which led to blindness. We draw attention to preventive measures that can potentially reduce permanent ocular damage from SJS.

INTRODUCTION

Stevens-Johnson syndrome (SJS) is a severe form of erythema multiforme, an acute inflammatory disease primarily affecting skin and mucous membranes.¹ In Malawi, manifestations of SJS are commonly seen in human immunodeficiency virus (HIV)–infected patients receiving nevirapine-based antiretroviral therapy (ART) and/or cotrimoxazole preventative treatment. Approximately 500,000 patients have received these medications within the national ART program since 2004.² Malawi has recently followed the World Health Organization guidelines to start ART earlier in the course of HIV infection because the CD4 cell threshold for starting ART has increased from 250 to 350 cells/ μ L. Patients with higher CD4 cell counts are at higher risk of nevirapine hypersensitivity, including patients with SJS.³ Ophthalmologists are familiar with SJS because 50% of patients have ocular complications,⁴ mainly involving eyelids, conjunctiva, and corneas,⁵ that can result in severe ocular damage. We describe a patient with SJS in whom severe ocular complications developed soon after initiation of nevirapine-based ART and cotrimoxazole preventive treatment, which eventually led to blindness.

CASE REPORT

A 25-year-old man came to our hospital because of rapidly progressing loss of visual acuity with a presenting vision of correct light projection in both eyes. He was HIV positive and was receiving treatment for tuberculosis. In August 2012, he began cotrimoxazole therapy one week before initiation of first-line ART with the standardized regimen for adults (stavudine, lamivudine, and nevirapine). After two weeks, SJS/toxic epidermal necrolysis (TEN) developed in the patient. Foreign body sensation in both eyes was present from the outset. At admission approximately six weeks after onset of SJS, we diagnosed a severe lid margin inflammation with advanced symblephara, mild chemosis, and conjunctivitis and a rapidly progressive conjunctivization of the cornea (Figures 1 and 2).

Full-size epithelial defects with advanced corneal thinning developed in the patient. Both anterior chambers were shallow, and appeared hazy because of severe intraocular inflammation. Iris, lens, and fundus were not accessible for examination by slit lamp. Over the course of two weeks, conjunctivization progressed despite systemic antibiotics and local therapy with ofloxacin, povidone iodine, and atropine eye drops. He turned blind (no perception of light) within two weeks of admission, possibly from an incurable endophthalmitis of unknown origin.

DISCUSSION

Several drugs have been reported to trigger ocular complications from SJS/TEN in Africa. Saka and others reported that antibacterial sulfonamides (50.6%) were most common used in Togo, followed by nevirapine (23.6%), non-steroidal anti-inflammatory drugs (5.6%), and anti-epileptic medications (3.4%). In 89 patients, they described few ocular complications: blindness occurred in three patients and moderate dry eye syndrome occurred in one patient.⁶ A study in Benin of seven patients with SJS/TEN reported one patient with ocular complications caused by ART. The other six patients had SJS/TEN secondary to ingestion of sulfadoxine-pyrimethamine, but no eye complications.⁷ Stevens-Johnson syndrome and TEN do not appear to have a racial or geographic predilection. The incidence of SJS is believed to be 6 cases/1,000,000 population/year and that of TEN is 1–2 cases/1,000,000 population/year.^{8,9} In Malawi, severe cutaneous reactions to sulfadoxine-pyrimethamine and cotrimoxazole have been reported by Gimnig and others, who did not report any ocular complications.¹⁰

In our experience, there is insufficient awareness of eye complications that can result from SJS/TEN among HIV-positive patients receiving ART in Malawi. Patients with SJS/TEN are often not reviewed by an ophthalmologist or an eye care specialist during the acute stage of the disease. Therefore, severe eye sequelae may not be recognized. This finding leads to insufficient care and treatment and a potential for severe ocular complications, including blindness. Many investigators have emphasized that consultation by an ophthalmologist is essential within the first days of acute SJS/TEN to avoid lid margin keratinization and tarsal scarring, together with lipid tear deficiency, which lead to blink related micro-trauma and subsequent corneal damage.¹¹ Some investigators have suggested

*Address correspondence to Markus Schulze Schwering, College of Medicine, University of Malawi, PO Bag 360, Blantyre 3, Malawi. E-mail: mssoculus@web.de

Photo 1 Face of Malawian patient with SJS - 6 weeks after onset; visual acuity: light perception in both eyes

Photo 2 Trunk of Malawian patient with SJS - 6 weeks after onset

FIGURE 1. 1, Face of a Malawian patient with Stevens-Johnson syndrome (SJS) six weeks after onset. 2, Trunk of a Malawian patient with SJS six weeks after onset.

Photo 3 Malawian SJS patient: eyes overview; severe conjunctivalization, corneal decompensation

All photos 6 weeks after SJS onset

Photo 4 Malawian SJS patient: slitlamp right eye

Photo 5 Malawian SJS patient: slitlamp left eye

FIGURE 2. 3, Overview of the eyes of a Malawian patient with Stevens-Johnson syndrome (SJS). 4 and 5, Slitlamp views of the right and left eye of a Malawian patient with SJS.

that amniotic membrane transplantation (AMT) in the acute stage is essential to prevent sight-threatening complications.^{11–13}

We expect to see an increase in the incidence of SJS/TEN as more patients with higher CD4 cell counts start ART, following changes in the CD4 cell threshold in the Malawi and World Health Organization ART guidelines. Patients with higher CD4 cell counts are at higher risk of nevirapine hypersensitivity syndromes, including SJS.³ It is important that ART providers in Malawi and other countries in the region who use nevirapine based first-line ART are aware of the severe eye complications associated with SJS/TEN, so that they can refer patients in a timely fashion or start appropriate preventive and therapeutic measures if referral is not possible.

Providers of ART in rural settings should know how to treat acute eye complications with topical lubricants, topical steroid eyedrops, and lysis of developing symblephara by using a sterile glass rod. Vitamin A ointment may be used for corneal re-keratinization. The benefit of peeling pseudomembranes is unproven. Keratitis must be treated early with antibiotics because it can easily develop into a corneal ulcer, as seen in our patient. Oral mucosal grafts are useful in more advanced cases such as severe corneal ulceration.

Steroid pulse therapy at disease onset could be of therapeutic importance in preventing ocular complications. Topical betamethasone also shows promise for preventing corneal epithelial stem cell loss in the limbal region and cicatricial changes.¹⁴ Satake and others reported that cultivated oral mucosal epithelial sheet transplantation (COMET) can offer a viable and safe alternative in the reconstruction of a stable ocular surface.¹⁵ Early intervention with AMT could have prevented the severe outcome in our patient. Although formal evidence is lacking, Gregory described the benefits of early AMT as the treatment of choice for acute SJS/TEN with severe ocular complications,¹² but it has not yet been introduced in Malawi because of the need for technical expertise, risk of transmission of infections, and the requirement of storing material at -80°C , which are major challenges.

We report a patient from Malawi in whom blindness developed after SJS, which developed after initiation of nevirapine-based ART and cotrimoxazole preventive treatment. More awareness of the risk of severe eye complications in this setting may lead to earlier recognition and treatment of eye complications associated with SJS. Amniotic membrane transplantation could further improve outcomes, although a formal evidence base is lacking and operational challenges exist.

Received December 15, 2012. Accepted for publication March 3, 2013.

Published online April 8, 2013.

Acknowledgments: We thank Else Kröner-Fresenius Stiftung for supporting the College of Medicine, Blantyre, Malawi. The American Committee on Clinical Tropical Medicine and Travelers' Health (ACCTMTH) assisted with publication expenses.

Authors' addresses: Markus Schulze Schwing and Petros Kayange, Department of Ophthalmology, College of Medicine, University of Malawi, Blantyre, Malawi, E-mails: mssoculus@web.de and

petroskayange@yahoo.com. Joep van Oosterhout, Department of Medicine, College of Medicine, University of Malawi, PO Bag 360, Blantyre 3, Malawi, E-mail: joepvanoosterhout@gmail.com. Martin Spitzer, Department of Ophthalmology, University Eye Hospital, Tübingen, Germany, E-mail: spitzko@googlemail.com.

REFERENCES

1. Elias PM, Fritsch PO, 1989. Erythema multiforme. Fitzpatrick TB, Eisen AZ, Wolff K, editors. *Dermatology in General Medicine*. New York: McGraw-Hill, 555–562.
2. Department of HIV and AIDS Ministry of Health, 2012. *Quarterly Report of the Antiretroviral Treatment Programme in Malawi with Results up to July 31, 2012*. Lilongwe, Malawi: Malawi Ministry of Health, Department of HIV and AIDS.
3. Kiertiburanakul S, Sungkanuparph S, Charoenyingwattana A, Mahasirimongkol S, Sura T, Chantratita W, 2008. Risk factors for nevirapine-associated rash among HIV-infected patients with low CD4 cell counts in resource-limited settings. *Curr HIV Res* 6: 65–69.
4. Stevens AM, Johnson FC, 1922. A new eruptive fever associated with stomatitis and ophthalmia. Report of two cases in children. *Am J Dis Child* 24: 526.
5. Mondino BJ, 1990. Cicatricial pemphigoid and erythema multiforme. *Ophthalmology* 97: 939–952.
6. Saka B, Kombaté K, Mouhari-Toure A, Akakpo S, Tchangaï-Walla K, Pitché P, 2010. Stevens-Johnson syndrome and toxic epidermal necrolysis in a teaching hospital in Lomé, Togo: retrospective study of 89 cases. *Med Trop* 70: 255–258.
7. Ukponmwan CU, Njinaka I, Ehimiye ET, 2010. Ocular complications of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Trop Doct* 40: 167–168.
8. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Fléchet ML, Girre JP, 1990. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug etiology in France, 1981–1985. *Arch Dermatol* 126: 37–42.
9. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, 1995. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 333: 1600–1607.
10. Gimnig JE, MacArthur JR, M'ang'mbe M, Kramer MH, Chizani N, Stern RS, Mkandala C, Newman RD, Steketee RW, Campbell CH, 2006. Severe cutaneous reactions to sulfadoxine-pyrimethamine and trimethoprim-sulfamethoxazole in Blantyre District, Malawi. *Am J Trop Med Hyg* 74: 738–743.
11. Di Pascuale MA, Espana EM, Liu DT, Kawakita T, Li W, Gao YY, Baradaran-Rafii A, Elizondo A, Raju VK, Tseng SC, 2005. Correlation of corneal complications with eyelid cicatricial pathologies in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome. *Ophthalmology* 112: 904–912.
12. Gregory DG, 2011. Treatment of acute SJS and TEN using amniotic membrane: a review of 10 consecutive cases. *Ophthalmology* 118: 908–914.
13. Shamma MC, Lai EC, Sarkar JS, Yang J, Starr CE, Sippel KC, 2010. Management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis utilizing amniotic membrane and topical corticosteroids. *Am J Ophthalmol* 149: 203–213.
14. Araki Y, Sotozono C, Inatomi T, Ueta M, Yokoi N, Ueda E, Kishimoto S, Kinoshita S, 2009. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Am J Ophthalmol* 147: 1004–1011.
15. Satake Y, Higa K, Tsubota K, Shimazaki J, 2011. Long-term outcome of cultivated oral mucosal epithelial sheet transplantation in treatment of total limbal stem cell deficiency. *Ophthalmology* 118: 1524–1530.