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Stevens-Johnson Syndrome (SJS) - Toxic Epidermal Necrolysis (TEN) Overlap due to Cotrimoxazole in a Patient with Acquired Immune Deficiency Syndrome (AIDS): A Case Report

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ABSTRACT

Background: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome are rare, immunologically-mediated skin reactions with severe dermatologic features that are usually triggered by exposure to drugs and/or other external agents. SJS manifested as less than 10% of the body surface area (BSA) affected in forms of skin detachment, whereas more than 30% involvement occur in TEN. Cases with BSA involvement in between mentioned range (10-30%) are then defined as of SJS–TEN overlap syndrome. SJS-TEN morbidity typically manifests at 40 years of age or older. Higher mortality was found in SJS/TEN overlap patients rather than SJS. The therapy given to SJS/TEN overlap patients is supportive therapy according to complaints. The most important thing is to stop drugs that are suspected to be triggers.

Case presentation: A 59-year-old male with SJS-TEN overlap, manifested as maculopapular rash with detachment of epidermis and a positive Nikolsky sign about 25% BSA. The patient had a history of taking cotrimoxazole for toxoplasmosis therapy before symptoms appeared. Multiple widespread lesions found all over the body, with maculopapular hyperpigmentation, black crust-covered erosion from the bullae, and numerous erosions on the lip mucosa covered in brown crusts. The management of this patient was supportive therapy and stop the suspected drug. Within a few weeks, the patient's condition improved without sequelae.

Conclusion: Overlapped SJS-TEN is cutaneous adverse reactions with immunologically-mediated dermatological disorders, with 10-30% BSA skin detachment. Management includes stopping all suspected cause, high dose steroid administration, along with supportive symptomatic therapy.

Keywords: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Human Immunodeficiency Virus, Acquired Immunodeficiency Syndrome

INTRODUCTION

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome are rare immunologically-mediated skin reactions with severe dermatologic features that are usually triggered by exposure to drugs and/or other external agents.[1] It manifests as blister formation with epidermal detachment; affecting less than 10% of the body surface

area in SJS, but over 30% in TEN. Patients with BSA involvement in between (10–30%) are classified as SJS–TEN overlap syndrome.[1] Clinically, SJS/TEN is defined by widespread distribution of macules (fat abnormal target lesions), preferentially involve the trunk. These lesions then quickly develop into a blistering condition affecting skin and mucosal surfaces.[2] It is associated with high mortality and morbidity. The exact pathogenesis of SJS/TEN is still nut fully understood, as it is related to an immunological response that triggers a cytotoxic cell-mediated response against keratinocytes, which results in a significant amount of apoptosis. Most common causative drugs that increase the risk of this disease are antibiotics (cotrimoxazole), anticonvulsants (carbamazepine, lamotrigine, pheno-barbital), allopurinol, Non-Steroid Anti Inflammation (meloxicam) and nevirapine. The duration from drug being administered to the reaction might vary from 4 to 28 days. Low-risk medications, however, can take up to eight weeks or even longer.[3]

SJS-TEN incidence is around 5:1.000.000 and 2:1.000.000 cases per year.[4] In Europe and USA, annual incidence is approximately one to six cases per 1 million patients with male to female ratio of 6:10.5 It may occurs at any age, but higher incidence found in people above 40 years. Rate of mortality was nearly 10% in SJS, 30% in SJS/TEN overlap, and could be as high as 50% in TEN.[5]

While SJS/TEN is known to be caused by immune-mediated hypersensitivity reaction, immunocompromised patients are known at risk for SJS/TEN reaction, especially those with infection by human immunodeficiency virus (HIV). Acquired Immune Deficiency Syndrome (AIDS) caused by HIV was reported between 0.95 to 1 per 1000 population per year.[6] A study from South African hospital reported SJS/TEN occurred in HIV patients has increased from 40% to 69% from 2004 to 2006.[5] In HIV patient, the most common drugs inducing SJS/TEN is sulphonamide antibiotics (38%) and antiretroviral known as nevirapine (20%).[4] The principal management of SJS/TEN is to stop all drugs suspected, and supportive treatment such as immunosuppression with corticosteroids.[7]

In this article, we present case of an AIDS patient who developed SJS-TEN overlap syndrome after treated with a sulphonamide antibiotic, Cotrimoxazole.

CASE REPORT

A 59-year-old male patient admitted to Wangaya Regional Hospital with maculopapular rash almost over his entire body. Alloanamnesis reported the lesions showed up 2 weeks after taking cotrimoxazole for toxoplasmosis treatment. Patient complained fever, burning sensation, as well as red spots with blister on his body, face, extremities, lips, anus, and genital mucosa. Few days later, patient felt weak because of swallowing difficulty 2 days prior to admission. Patient was diagnosed with HIV and Toxoplasmosis 1 month before admission after experiencing weakness, cough and headaches for the past 1 month. The patient also experienced weight loss of 20 kg over 2 months. History of diabetes, or cardiovascular disease was denied. Patient also denied similar previous complaint or allergic history to medicine before. There were also no atopic history in his family member.

From physical examination, patient came with GCS E3V5M6, blood pressure of 100/70 mmHg, with heart rate of 76 bpm, axillary temperature 36.7°C, and respiration rate 24 times per minute. From head-to-toe assessment, there are erosion covered with brown-colored crust on patient's lips, multiple erosion on anal and genital mucosa. On dermatological state, face, chest, abdominal, both upper and lower extremities, there are multiple widespread macula hyperpigmentation. There also multiple bullae and with erosion covered with blackish crust in some areas. Nikolsky sign is positive, with BSA involvement approximately 25%.

Laboratory examination showed white blood cells 3.26 x 10^3/uL, hemoglobin levels of 10.7 g/dL, hematocrit levels of 30.1, % platelet 215x10^3/uL, albumin 2.9 g/dL, SGPT 34 µ/L, SGOT 32 µ/L, random blood glucose 91 mg/dL, urea 40 mg/dL, creatinine 1.3 mg/dL, sodium 127 mEq/L, potassium 4.0 mEq/L, and chloride 93 mEq/L. The patient assessed as SJS/TEN overlap with suspected cause of cotrimoxazole. Patient was treated in cooperation with internal medicine specialist.

The patient was hospitalized and asked to stop taking the suspected drug. The patient received methylprednisolone 125 mg intravenously (IV) two times daily for 3 days, and gradually tapered to 125 mg methylprednisolone IV once daily for 3 days. Other therapies included esomeprazole 40 mg IV once daily, gentamicin 80 mg intravenously twice daily, 10 mg of oral loratadine once daily. Antiviral drugs for AIDS therapy are still given every 10 AM. For topical treatment, wound compress with 0.9% NaCl twice a day for 10-15 minutes was done before administering ointment of gentamicin cream all over skin lesion twice a day. For oral hygiene, patient was given 0.2% aseptic liquid after every meal.

During follow-up period, new lesions were not found, and lesions started to heal. Patient can eat and drink normally. From dermatological status, erosions in the face, abdominal, and all extremities are covered with black crust, as well as the lip, anal, and genital mucosa erosion.

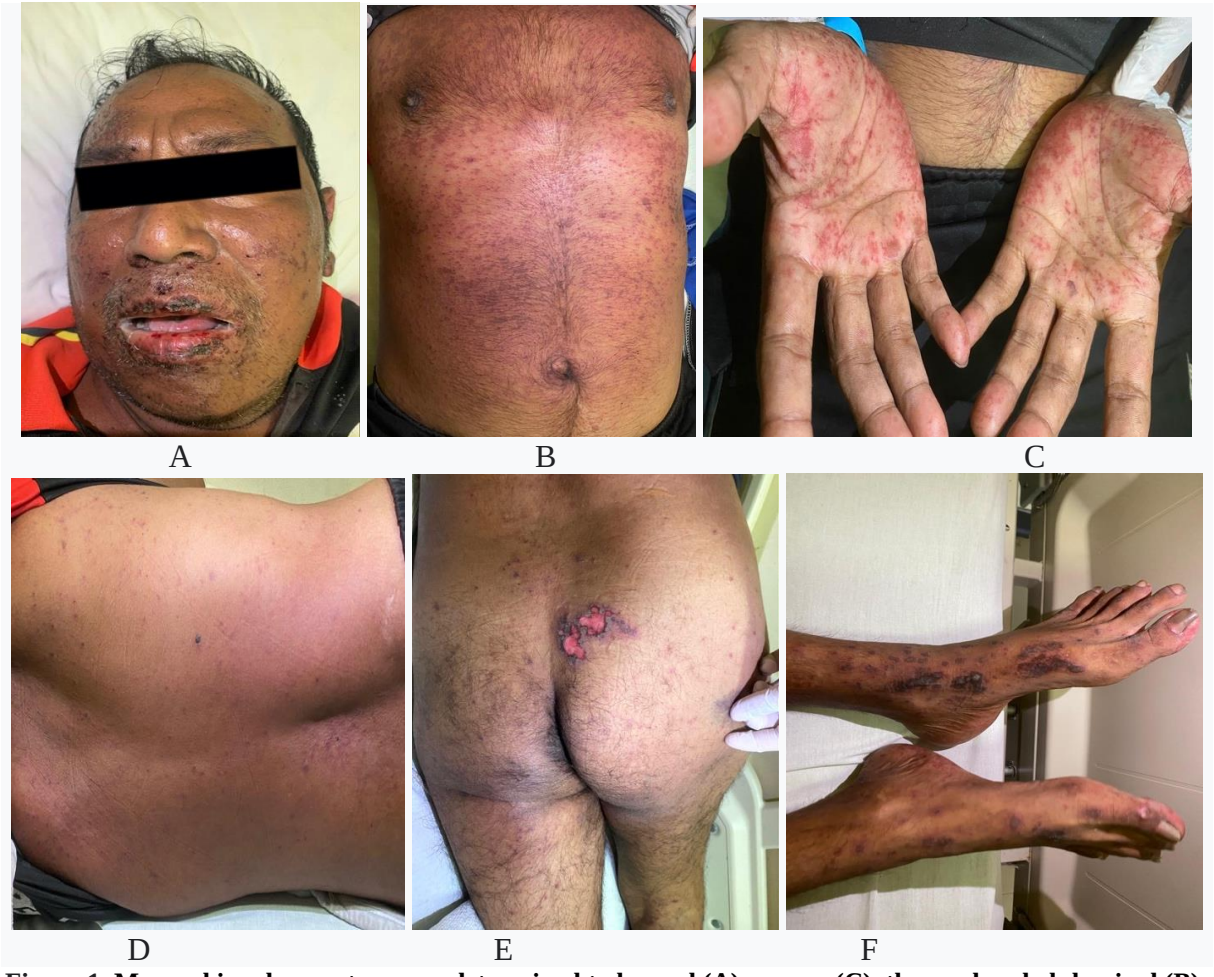

Figure 1. Mucosal involvement was predetermined to be oral (A), manus (C), thoracal and abdominal (B), lumbal (D), anal (E), pedis (F). The rash includes mucosal erosions and crusting with a Nikolsky's sign (+). Approximate BSA involvement is around 25%.

DISCUSSION

SJS-TEN are considered the most severe of drug hypersensitivity reactions, with antibiotics being the highest risk factor.[8] Epidermal detachment affects <10% of BSA in SJS, while TEN requires >30% involvement. Cases with BSA involvement in between those ranges are classified SJS–TEN overlap syndrome.[1] The period between first suspected drug administration and development of reaction varies between 4 until 28 days, or even more than 8 weeks in lower risk drugs.[3] In this case, the lesion appear 2 weeks after taking cotrimoxazole for toxoplasmosis treatment. The most common drug that increasing the risk of this disease are sulphonamide antibiotics (cotrimoxazole), anticonvulsants (carbamazepine, lamotrigine, pheno-barbital), allopurinol, Non-Steroid Anti Inflammation (meloxicam) and nevirapine. This finding is similar with systematic review and meta-analysis conducted by Lee et al which reported 28% incidence of SJS/TEN were associated with antibiotics. Among SJS/TEN caused by antibiotics, approximately 32% of cases are caused by the sulphonamides (cotrimoxazole), while penicillin causes 22% incidence, followed by cephalosporins (11%), quinolones (4%), and lastly macrolides (2%).[9]

Co-trimoxazole belongs to the sulphonamide class of antibiotics. Sulphonamides are compounds derived from p-aminobenzene sulphonamide (sulphanilamide) and include all substances with the SO2NH2 group. Sulphonamides are divided into two categories: antibiotic sulphonamides and non-antimicrobial sulphonamides. Sulphonamide antibiotics have an aromatic amine group on N4 position and a 5 or 6- membered aromatic heterocyclic ring with ≥1 nitrogen at the sulfonamide-N1. These metabolites are believed to cause reactions that are not mediated by IgE. The N4 of sulphonamide antibiotics is acetylated to produce N4-acetyl sulfamethoxazole. Reactive nitroso compounds, which can directly induce cytotoxicity or attach to T cells and trigger an immunological response that results in diseases like SJS or TEN, can be produced by further oxidizing the N4-hydroxylated metabolite. Since non-antimicrobial sulfonamides lack aromatic amines, they are unable to produce these reactive metabolites.[8]

This patient complaint of fever, burning sensation, also appear red spot with blister on the body, face, extremity, lips, anal and genital mucosa. On physical examination, positive Nikolsky sign was found with detachment covering 25% of BSA. Typically, skin lesions begin as erythematous macules and atypical target lesions, which may confluence and develop blisters. Mucous membrane involvement was indicated by burning or stinging in the eyes as well as pain during swallowing or peeing. Large patches of exposed, red, occasionally seeping dermis are revealed when the Nikolsky sign (dislodgment of the epidermis by lateral pressure) is positive on the erythematous zone and displays necrotic epidermis that is easily detached.[2]

Risk factors such as HIV infection, genetics, underlying immunologic disease, cancer, radiation therapy, and UV light exposure are all associated with the development of SJS-TEN. HIV infected patients may have a 100-fold greater risk of experiencing a drug reaction that triggers SJS/TEN compared with the general population. The significant incidence of SJS-TEN in immunocompromised patients is might be caused by several factors, including polypharmacy in HIV treatment, slow drug acetylation, lack of glutathione, alteration of lymphocyte, and the cytotoxic metabolite of drugs used in HIV therapy. Concomitant infections, such as tuberculosis may worsen the condition as the patient needs to consume more variety of drugs, which can increase susceptibility to SJS/TEN.[10,11] This patient have comorbidities of HIV infection that significantly increases the risk of SJS/TEN.

The most important management of SJS-TEN is discontinuation of suspected precursor medication, and supportive

treatment.[7] In the treatment of SJS-TEN, a multidisciplinary partnership between experts from different medical specialties was recommended.[12] Despite being controversial due to its significant risk of infection, systemic corticosteroids are nonetheless often utilized in these cases, even in individuals with impaired immune systems.[12] In the early stages of the condition, systemic corticosteroids were believed to be able to stop the disease from spreading, particularly when given as an intravenous pulse over a few days.[2] There isn't yet a gold standard for wound treatment. Dermatologists and internists worked together collaboratively to treat the patient in this case. Patient received methylprednisolone 125 mg IV twice daily for 3 days, and gradually tapered to 125 mg methylprednisolone IV once daily for the next 3 days. Other supportive therapies were also given, including esomeprazole 40 mg IV once daily, gentamicin 80 mg IV twice daily, and loratadine 10 mg orally once daily. Antiviral drugs for AIDS therapy are still given every 10 AM. For topical treatment, wound compress with 0.9% NaCl twice a day for 10-15 minutes was done before applying gentamicin cream all over skin lesion twice a day.

CONCLUSION

We reported a SJS-TEN Overlap case which was suspected to be caused by cotrimoxazole in a 59 year-old man with HIV and toxoplasmosis infection. The diagnosis is made by clinically based on comprehensive anamnesis, physical examination and further lab assessment. Management of this patient was supportive therapy, stop the suspected drug and administering high dose systemic corticosteroid. Within a few weeks, patient's condition improved with no sequelae.

Declaration by Authors

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REFERENCES

1. Sousa-Pinto, B., Araújo, L., Freitas, A., Correia, O., & Delgado, L. Stevens–Johnson syndrome/toxic epidermal necrolysis and erythema multiforme drug-related hospitalisations in a national administrative database. Clinical and Translational Allergy 2018 Jan 22;8:2. https://doi.org/10.1186/s13601-017-0188-1
2. Mockenhaupt M, Roujeau JC. Epidermal Necrolysis (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis). In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS, eds. Fitzpatrick's Dermatology. 9th Ed. New York: Macgraw-Hill. 2019: 733-48.
3. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: An Update. Am J Clin Dermatol. 2015 Dec;16(6):475-93. https://doi.org/10.1007/s40257-015-0158-0.
4. Suwarsa O, Yuwita W, Dharmadji HP, Sutedja E. Stevens-Johnson syndrome and toxic epidermal necrolysis in Dr. Hasan Sadikin General Hospital Bandung, Indonesia from 2009-2013. Asia Pac Allergy. 2016 Jan;6(1):43-7. https://doi.org/10.5415/apallergy.2016.6.1.43.
5. Citra BD, Masri R. STEVENS JOHNSON SYNDROME PADA PASIEN HIV. Hum Care J. 2020;5(2):545. http://dx.doi.org/10.32883/hcj.v5i2.764
6. Sari LG, Pemayun TD. Stevens-Johnson Syndrome (SJS)-Toxic Epidermal Necrolysis (TEN) overlap in a 61-year old woman: A case report. Intisari Sains Medis. 2020 Aug 1;11(2):606-9. https://doi.org/10.15562/ism.v11i2.618
7. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, Rourke SB. Incidence of toxic epidermal necrolysis and Stevens-Johnson Syndrome in an HIV cohort: an observational, retrospective case series study. Am J Clin Dermatol. 2012 Feb 1;13(1):49-54. https://doi.org/10.2165/11593240-000000000-00000.
8. Khan DA, Knowles SR, Shear NH. Sulfonamide Hypersensitivity: Fact and

Fiction. J Allergy Clin Immunol Pract. 2019 Sep-Oct;7(7):2116-2123. https://doi.org/10.1016/j.jaip.2019.05.034.
9. Lee EY, Knox C, Phillips EJ. Worldwide Prevalence of Antibiotic-Associated Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. JAMA Dermatol. 2023 Apr 1;159(4):384-392. https://doi.org/10.1001/jamadermatol.2022.6378.
10. Chateau AV, Dlova NC, Dawood H, Aldous C. Outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in HIV-infected patients when using systemic steroids and/or intravenous immunoglobulins in Pietermaritzburg, South Africa. South Afr J HIV Med. 2019 Jul 4;20(1):944. https://doi.org/10.4102/sajhivmed.v20i1.944.
11. González Barajas AJ, Eyenith A, Torres M. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Epidemiology and Risk Factors. International Journal of Medical Science and Clinical Research Studies. 2023; 3(1), 31–34. https://doi.org/10.47191/ijmscrs/v3.
12. Le HG, Saeed H, Mantagos IS, Mitchell CM, Goverman J, Chodosh J. Burn unit care of Stevens Johnson syndrome/toxic epidermal necrolysis: A survey. Burns. 2016 Jun;42(4):830-5. https://doi.org/10.1016/j.burns.2015.12.001.

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