ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and potentially fatal hypersensitivity reactions that can be drug-induced, especially in patients with AIDS. This report aims to highlight the diagnosis and management of a patient with acquired immunodeficiency syndrome (AIDS) that consumed multiple drugs including anti-tuberculosis drugs that develop SJS.

Case presentation: A 30-year-old male patient with AIDS administered with chief complaints of burning sensation all over the bodies and erythematosus macules scattered across the stomach and back, followed by blisters distributed across the chest, back, face, lips, hands and feet, as well as genitals for 3 days. Patient was diagnosed with AIDS and under ARV medication since about 5 years ago and dan otrimoxazole for 9 months. Couple months before admission, patient was diagnosed with tuberculosis and under anti-tuberculosis treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE)) but stopped due to drug-induced hepatitis (DIH) which then changed to another regiment (streptomycin, levofloxacin, and ethambutol (SLE)) followed by another regiment (rifampicin, isoniazid and ethambutol (RHE)). The patient diagnosed with drug-induced SJS, however, in order to find out the SJS drugs inducer, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis (ALDEN) score as causality assessments tool was applied and rifampicin decided to be the precursor. The patient was managed for 13 days prior to discharge with improved condition.

Conclusion: Diagnosing process for drug-induced in patient with AIDS, in addition to multiple drugs consumption, is a challenge. A multidisciplinary approach and appropriate causality assessments tool should be considered before administering further management and medications.

Keywords: Stevens-Johnson syndrome, AIDS, tuberculosis, drug-induced.


INTRODUCTION

Stevens-Johnson syndrome (SJS) is a type of drugs hypersensitivity reaction, a variant of erythema multiforme, with high morbidity besides toxic epidermal necrolysis (TEN). SJS instigated by numerous factors (infection, drugs, and malignancy) which characterized by flaking epidermis and mucous membranes erosions.1,2 These disorders are distinguished predominantly by the degree of body surface area (BSA) involvement where TEN has more severe form, involving > 30% of BSA detachment, while <10% considered as SJS. However, an SJS/TEN overlap syndrome is diagnosed for intermediate cases.3,5

The incidence of SJS and TEN is approximately 5:1.000.000 and 2:1.000.000 cases per year, respectively.4 In Europe and USA, annual incidence of SJS is estimated to be 1-6 cases per 1 million patients which is less often in men (sex ratio of 0.6).1 Meanwhile, the prevalence in individuals with AIDS has been reported to be between 0.95 and 1 per 1000 per year.7 A study in a South African hospital showed the incidence of SJS/TEN mainly occurred in human immune virus (HIV) patients which increased from 40% to 69% in 2004 to 2006.5 More than 100 drugs had been associated with the occurrence of SJS/TEN in antibacterial sulfonamides, anticonvulsants, non-steroidal anti-inflammatory drugs, antimalarials, allopurinol, including herbal medicine.8,9 As for HIV patient, The most common drugs inducing SJS/TEN is antibacterial sulfonamides (38%) and antiretroviral known as nevirapine (20%).1,10

The management of SJS/TEN rests on three cornerstones namely, withdrawal of the precursor drug, active treatment, and supportive treatment.8,11 In some countries, systemic administration corticosteroids considered as contentious, and highly debatable for HIV patients due to the risk of further immunosupression.9,12 Here we report a case of patient with AIDS that developed SJS after treated with an anti-tuberculosis (TB) drug, rifampicin.
CASE PRESENTATION

A 30-year-old male patient with AIDS administered to the emergency room of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia with the chief complaint of burning sensation all over the bodies and erythematous macules scattered across the stomach and back for three days prior to admission. The erythematous macules followed by blisters distributed across the chest, back, face, lips, hands and feet, as well as genitals. The patient also complained of difficulty opening his mouth and swallowing due to immense pain, both eyes felt sore, reddish, and watery. A clear-whitish-colored discharge was secreted from his penis. A week before, the patient also complained about joint pain, fatigue, and loss of appetite. There was no fever, diarrhea, cough, dyspnea, or anosmia complaint.

The patient was diagnosed with AIDS since July 2015 and had been on anti-retroviral (ARV) treatment (lamivudine, tenofovir, and efavirenz), additionally, cotrimoxazole was given for approximately 9 months (August 2015 – April 2016) without any side effects. In April 2020, patient was diagnosed with pulmonary TB and anti-TB drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol HRZE) were prescribed only 27 days due to drug induced hepatitis (DIH) and then changed to streptomycin, levofloxacin, ethambutol (SLE) regiments for seven days (13th-20th May 2020) which the reintroduced to isoniazid (20th-27th May 2020) and rifampicin (3rd-10th June 2020). He took (R450 H300 E750) regiments since then.

On physical examination, the patient looked weak with normal vital signs and GCS. Hyperemic conjunctiva without secret production, hemorrhagic crust on the lips, and huge erythematous macules on the face without scale were found, but there was no jaundice, cyanosis, and dyspnea (Figure 1A). Thorax examination revealed widespread erythematous macules in the anterior and posterior with blisters (no squama) in several area. Abdominal examination showed a large erythematous macule without scale. As for extremities, there were large erythematous macules without scale all over the hands and feet, and several scattered black macules, but there was no edema (Figure 1B).

On the early laboratory tests (June 24th 2020) obtained hemoglobin (Hb) 10.4g/dL, white blood cell (WBC) 5x10^3/L, platelets 220x10^3/L, hematocrit (HCT) 31%, neutrophil 55.6%, lymphocyte 19.4%, random blood glucose 111 mg/dL, serum glutamic-oxaloacetic transaminase (SGOT) 100 U/L, serum glutamic pyruvic transaminase (SGPT) 95 U/L, blood urea nitrogen (BUN) 33 mg/dL, serum creatine 2 mg/dL, albumin 3.29, potassium (K) 4.5 mEq/L, sodium (Na) 137 mEq/L, chloride (Cl) 101 mEq/L, HbsAg non-reactive, antigen COVID-19 rapid test non-reactive, erythrocyte sedimentation rate (ESR) 98, pH 7.47, pCO₂ 21, pO₂ 122, HCO₃ 15.3, base excess (BE) -8.2, and SO₂ 99% free air. Electrocardiography (ECG) result was within normal limits and chest X-ray examination was within normal limits.

The patient was consulted to the Dermatovenereology Department with SJS and advised to stop all the current drugs (except ARV), followed by administration of intravenous dexamethasone 25 mg three times daily, intravenous gentamycin 80mg twice daily, oral cetirizine 10mg twice
daily, and normal saline compression on the skin lesion for 15 minutes twice a day. The patient also consulted to Pulmonology Department with pulmonary TB on anti-TB drugs with drug eruption suspected due to rifampicin and advised to stop the anti-TB drugs temporarily, which would later be restarted with desensitization the drug eruption improved.

The patient was diagnosed with drug induced SJS due to anti-TB drug (suspected rifampicin), acute kidney injury (AKI), AIDS on ARV, pulmonary TB on anti-TB drugs with DIH regimen (9RHE) advanced phase. In order to determine the inducer(s), we used ALDEN score as causality assessments tools (CAT) that showed rifampicin as the SJS inducer.

The patient was given high-calorie high protein liquid diet 1900 kcal/day, intravenous electrolyte fetal dextrose 1000ml/day, oral cetirizine 10mg, twice daily normal saline compression for 15 minutes on the skin lesion twice a day, continue ARV, and stop anti-TB drugs as the suspected drugs. Intravenous dexamethasone was not given considering the immunosuppressed condition and intravenous gentamycin was also not given due to the alteration of kidney function.

On the 2nd day of treatment, the patient still complained about fatigue, hotness and sore of the skin, crusts on the lips, and difficulty to eat due to pain when swallowing. Physical examination showed weakness, normal vital signs, erythematous macules were scattered all over the patient's face, body, and extremities, accompanied by several non-scaled blisters distributed on the chest and back as well as both arms. The laboratory tests results showed SGOT/SGPT 92/81, BUN/creatinine 23/1.7, albumin 3, calcium 8.0, Na/K/Cl 138/3.5/101, and C-reactive protein (CRP) 1.4 mg/L. The therapy was continued.

During 6th followed up, the patient felt better, there was no cough, dyspnea, or fever, but the skin itchiness subsided. The erythematous macule on the body got better, blisters began to cracked and peeled, crusts on the lips dried up, swallowing pain was healed and patient able to eat and drink. On physical examination, general condition was sufficient with normal vital signs. Laboratory test results showed SGOT/SGPT 54/59, albumin 2.8, BUN/creatinine 14/1.6, and Na/K/Cl 138/3.6/105.

Two days later the patient felt better, there was no cough, dyspnea, fever, and skin itching subsided. The erythematous macule improved, blisters dried and started to peeled off, no new blisters appeared. On physical examination, general condition was sufficient with normal vital signs.

A week of admission, the patient was planned to be discharged as a result of clinically improved skin lesions on the face (Figure 1C) and body (Figure 1D), but coughing and feverish complaints. On physical examination, vital sign was normal, but body temperature was increased (38°C), with SpO2 99% free air. COVID-19 screening procedure was conducted with total score of 9, probable case (4 point for being hospitalized, 4 points for having cough and fever, and 1 point for having AIDS as comorbids). SJS due to rifampicin and AKI were resolved. The patient still in hypoalbuminemia (2.8), AIDS on ARV, and pulmonary TB on anti-TB drugs DIH regimen (9RHE) advanced phase (stop). The patient was planned to undergo PCR swab and given additional therapies (oral paracetamol 3x500mg and oral N-acetyl cysteine 3x200mg).

On the 13th day, last day of admission, the patient felt better with no fever and shortness of breath with a little cough. Physical examination and vital signs were within normal limits, COVID-19 PCR yielded negative results. Laboratory tests evaluation showed Hb 9.7 g/dL, leucocyte 3.56 x 10³/L, platelets 205x10³/L, HCT 28.9%, neutrophil 55.8%, lymphocyte 21.1%, blood glucose 111 mg/dL, SGOT 38 U/L, SGPT 43 U/L, BUN 24mg/dL, creatine 1.2 mg/dL, albumin 3, procalciotin 0.20 ng/mL. The patient was discharged with oral fixed-dose combination ARV once daily, oral paracetamol 500 mg three times daily, oral N-acetyl cysteine 200 mg, three times daily, and oral cetirizine 10mg once daily.

**DISCUSSION**

Patients with HIV infection have a higher risk of drug reactions with 100 times more risk of developing SJS or TEN. SJS/TEN has been recorded between 0.95-1 per 1000 in PLWHA. Interestingly, this condition is still unexplained. However, polypharmacy, dysregulation of immunity, associated contagions, and genetic polymorphisms intricate in explicit drug metabolism possibly contribute. Several medications such as anticonvulsants, antibiotics, NSAIDs, allopurinol, and antipsychotic drugs, analgesic–antipyretic drugs (acetaminophen), anti-TB drugs (rifampicin, ethambutol, isoniazid, and pyrazinamide) and anti-HIV remedies (nevirapine, lamivudine, and zidovudine) proved as common SJS/TEN-inducers.

Determining the causative drugs in SJS/TEN is challenging. The causative drug identification method is still not standardized, but history taking is still acceptable. Exposure tests considered unethical due to the risk of inducing severe relapses. However, several causality assessment tools (CAT) can be used to determine the causative drugs such as Naranjo, Liverpool, and ALDEN. Although these tools need an inclusive history, including exposure time, adverse drug reaction (ADR) symptoms onset, prior reactions to analogous prescription, and other related risk factors. In this case, we use ALDEN due to its highest reliability. We found that FDC ARV had been taken for five years without complaints, there for it was excluded. Rifampicin was taken for 27 days and stopped because the patient had DIH, then readministered about a month later until finally there were complaints of erythematous macules accompanied by burning sensation in the body and eye mucosa and genitalia 3 days before admission (18 days). However, when the drug was discontinued, no new lesions appeared. It was readministered after the patient was discharged and he complained of burning sensation and itchy skin (ALDEN score 6 (very probable)). As for isoniazid it was discontinued due to DIH, reintroduced and discontinued again, no new lesions appeared, later it was re-administered (levofloxacin, ethambutol, and isoniazid), patient had no complaints (ALDEN score was -3 (very unlikely)). Ethambutol was given since the beginning of pulmonary TB treatment and re-administered after the patient was discharged with no complaints at (ALDEN score -4 (very unlikely)). Cotrimoxazole was given for eight months in 2015 without
any complaints. The patient had taken the drug for 11 days before the symptoms appeared, when it was discontinued, there was no additional new lesions, and no complaints when it was re-administered (ALDEN score was 4 (probable)). We conclude that the SJS in this patient was induced by rifampicin.

Three cornerstones of managing the SJS/TEN are immediate termination of consumed medicines, active management, and supportive procedures. First, identifying the causative drugs is difficult due to the unavailability of appropriate laboratory procedures. Nevertheless, A careful history of recent administrated drugs (about 4 weeks) can be an alternative, which is known as a risk drug for SJS/TEN. What makes it difficult is that sometimes patients take more than one drug simultaneously, so it is recommended to discontinue all drugs.8 Our patient was asked to discontinue all drugs he had recently taken except for ARVs. The drugs were then identified using the ALDEN score to determine the causative drugs and rifampicin was determined with a score of 6.

The second approach is by giving an active treatment that aims to either prevent the worsening of the disease, stabilize the patient's homeostasis, and fend of bacterial invasion in the progression phase, or to induce reepithelization in regression phase. Several immunosuppressive treatments offer a beneficial effect in SJS/TEN.8 Although systemic administration of corticosteroids, especially for PLWHA, is still highly debatable in many countries due to the risk of further immunosuppression, many studies support it in SJS/TEN. In conclusion, it is a double-edged sword as treatment. Early administration of high-dose corticosteroids (oral methylprednisolone 1-2 mg/kg/day) in SJS/TEN can reduce skin impairment, increase recovery rate, and long-lasting sequelae. Rapid tapering is designated once progression stops.8 12 In this patient, corticosteroid administration was advised by Dermatovenereology Department but considering the patient's condition which already in a state of immunosuppression due to his underlying disease (AIDS), it will aggravate the immunosuppressant condition, so corticosteroid was not given. Corticosteroid administration can increase the risk of secondary bacterial infection in SJS patients. Antibiotics are recommended at the signs of secondary infection and it is proven that bacteria are present in the results of bacterial or fungal cultures in the specimens (skin, mucosal erosions, blood, and sputum). Administration of antibiotics must be done rationed because it is worried to introduce in a drug-specific intolerant individual.8 However, there is no sign of secondary bacterial infection on patient's skin lesion. Therefore, no corticosteroid or antibiotics was not given.

The regulation of fluid and electrolyte balance should also be of particular concern. Body fluid loss in SJS/TEN is chiefly caused by evaporation from skin erosions which uppermost in the progression phase can generate fluid and electrolyte imbalances. Therefore, several conditions (BP, HCT, blood gases, electrolytes, and proteins serum) are crucial to be monitored and accustomed.8 Fluid management in SJS/TEN cases is different from burn patients, though the area of skin lesions is the same, which is advised to use fluids containing electrolytes (0.7 mL/kg/% BSA) and albumin (5% human albumin, 1 mL/kg/% BSA).18 20 The purpose of fluid administration is to maintain urine production of 0.5-1 mL/kg/hour.19 21 These are crucial to preserving urine production at 0.5-1 mL/kg/hour. We considered water loss due to evaporation from skin erosions caused alteration in this patient's kidney function although there was no electrolyte imbalance. The patient was given IVFD Asering 1000ml/24 hours (patient can drink up to 1000ml a day), high-calorie high protein soft diet 1900kcal/day. Because only mild hypoaalbuminemia was found, the patient was not given albumin infusion. The patient’s daily urine output is about 1000ml.

The score of toxic epidermal necrolysis (SCORTEN) scale is a tool to score the severity rate for SJS/TEN that includes 7 equal predictive factors (range 0-7).21 The total score is used to predict the mortality rate in hospital that should be obtained at the initial 24 hours and repeated if the patient's condition deteriorates in the first 5 days.22 Based on SCORTEN, this patient met two parameters at admission: serum urea >10 mmol/L and serum bicarbonate < 20 mmol/L. Therefore, the probability of death in this patient is 12.1%, which means that 12 out of 100 patients with SJS conditions such as this patient can die. This patient was discharged after 13 days of treatment with dry and peeled skin lesions, no longer complain of pain, and good intake. Patient was asked to go to pulmonology for adjusting anti-tuberculosis drug.

CONCLUSION
A patient with AIDS on 5-year ARV had been reported with drug-induced SJS due to anti-TB drug (rifampicin). ALDEN score was used to determine the suspected drugs. Drug withdrawal, active treatment, and supportive treatment were offered without corticosteroid administration. The patient showed clinical improvement. The patient was discharged after thirteen days of treatment and continued therapy on an outpatient basis.

PATIENT CONSENT
The patient signed informed consent and agreed that the case would be published in an academic journal.

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REFERENCES


