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Case Report

Herbal-induced Stevens-Johnson syndrome with oral involvement and management in an HIV patient

S. Suniti and Irna Sufiawati
Departement of Oral Medicine
Faculty of Dentistry Universitas Padjadjaran
Bandung - Indonesia

ABSTRACT

Background: *Stevens-Johnson syndrome (SJS) is an immune complex-mediated hypersensitivity reaction affecting the skin and mucous membranes. Patients infected with human immunodeficiency virus (HIV) are at increased risk of developing SJS which is predominantly caused by an adverse reaction to medications, including herbal varieties. In recent years, the consumption of herbal medicines has increased, while their safety remains a matter for investigation.* ***Purpose:*** *The purpose of this case report is to explain the occurrence of SJS caused by herbal medicine.* ***Case:*** *A 43-year-old male patient with body-wide skin erosion was referred to the Department of Oral Medicine and subsequently diagnosed with Stevens-Johnson syndrome due to his consumption of a herbal medicine containing zingiber rhizoma, coboti rhizoma, asari herbal and epimedi. The patient's chief complaints included difficulty when opening the mouth, dysphagia and excessive production of saliva continuously contaminated with blood and sputum. Extraoral examination showed a sanguinolenta crust on the lips. Intra oral examination of oral mucous showed erosive lesions with bleeding and pain. A HIV test performed at a Clinical Pathology Laboratory was positive for antibodies against HIV with a CD4 cell count of 11 cells/ml.* ***Case management:*** *Treatment consisted of the administering of NaCl 0.9 %, hydrocortisone 0.1% and Chlorhexidine digluconate 0.12% for 12 days.* ***Conclusion:*** *SJS can be caused by herbal medicine and it is essential to be aware of the latter's potential adverse effects, especially in immunocompromised patients. Symptomatic management of oral lesions should be planned as an early intervention in order to decrease morbidity and mortality in SJS patients.*

Keywords: *Herbal medicine; HIV management; Stevens-Johnson syndrome*

Correspondence: Irna Sufiawati, Department of Oral Medicine, Faculty of Dentistry Universitas Padjadjaran, Jl. Sekeloa Selatan no.1 Bandung 40132, Indonesia. E-mail:irna.sufiawati@fkg.unpad.ac.id

INTRODUCTION

Stevens-Johnson syndrome (*SJS*) is an immune-complex-mediated hypersensitivity reaction affecting the skin and mucous membranes first described by Dr. Stevens and Dr. Johnson in 1922 as an acute mucocutaneous syndrome suffered by two young boys. The condition is characterized by mucocutaneous tenderness, hemorrhagic erosions, erythema and severe epidermal detachment presenting as blisters in areas of denuded skin.[1–5] SJS features blister-sores often referred to as Toxic Epidermal Necrolysis (TEN) which is categorized according to the surface area of the body affected by epidermolysis, i.e. SJS (affected body surface area <10%), SJS/TEN overlap (10–30%) and TEN (>30%).

The SJS ratio that occurs between males and females is 2:1 with a mortality rate of 5.4%.[6] The incidence rate of herbal medicine-induced SJS in China is 2.5%, in Malaysia it is 7.5%, while in Singapore and the Philippines it stands at 3.5%.[6] Other studies have shown that the majority of herbal medicine-induced SJS in HIV patients occurred in females (64.7%).[7] Mortality resulting from SJS depends on the extent of the body area affected and other accompanying conditions such as secondary infection and sepsis. HIV infection, increasing age, chronic conditions, hematological malignancy (non-Hodgkin's lymphoma and leukemia) and renal failure were also associated with SJS/TEN and mortality.[8,9]

Patients infected with human immunodeficiency virus (HIV) are at an increased risk of developing SJS which is

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reported to occur 100 times more frequently than in non-HIV patients. The incidence rate of SJS patients infected with HIV ranges from 40% to 69%.[10–13] The mortality rate of SJS in individuals infected with HIV is 1:100.000, while SJS mortality rates reported in the literature range between 10% and 75%.[1,12] HIV patients suffer dysregulation of T and B lymphocytes within the immune system. Certain multifactorial changes including drug metabolism, oxidative stress, cytokine profile, hyperactivation of the immune system and genetic factors are suspected of playing a role in this mechanism.[6]

The etiology of SJS in HIV patients is predominantly a drug-induced reaction including antituberculosis drugs, sulphonamides, anticonvulsants and antiretrovirals (nevirapine).[1,10,13] The pathophysiology of drug hypersensitivity in HIV is multifactorial and related to changes in drug metabolism, dysregulation of the immune systems (immune hyperactivation, patient cytokine profile), oxidative stress, genetic predisposition, NSAIDS and viral factors such as Epstein-Barr virus and cytomegalovirus infections.[13] Herbal medicines are drugs and may, therefore, cause severe adverse drug reactions.[6] SJS in HIV patients occurs most often due to several reactions to drugs, including herbal medicines.[14]

Herbal medicine consumption has recently been increasing. However, the non-observing of regulations is still being investigated. Herbal medicinal products containing mixed herbs (36.0%) as well as those administered orally (63.2%) predominate. The most frequent reactions were urticaria and rash (49.2%), urticaria (15%) and rash erythematous (13.4%), while anaphylactic reactions accounted for 9.5 %.[15,16]. Many patients believe that herbal medicines produce fewer side-effects and, therefore, often believe them to be safe. In SJS patients suspected of suffering from herbal medicine-induced etiology, it is very difficult to identify the specific medicine causing the hypersensitivity because most patients consume a mixture of herbal medicines.[11,17–21]

A diagnosis of herbal medicine-induced SJS in HIVpatients is reported here in addition to a literature-based description of SJS related to the characteristics and criteria used in both its diagnosis and oral treatment.

Table 1. The results of antimicrobial suspectibility testing

Microbiological examination		
Cultures microbiology		
Specimen	:	Sputum
Identification		
Isolate I	:	*Streptococcus qordonii*
Suspectibility		
Ampicillin	:	Intermediate
Clindamicin	:	Resistent
Tertracyclin	:	Resistent
Cefritriaxone	:	Suspectible
Cefotaxime	:	Suspectible
Levofloxacin	:	Suspectible
Linezolid	:	Suspectible

CASE

A 43-year-old man was diagnosed by the Department of Dermatology with multiple drug- induced SJS (herbal medicine, doxycycline, paracetamol, amoxycillin clavulanic acid). The patient was also diagnosed as suffering from HIV infection. The patient was referred to the Department of Oral Medicine with painful oral sensations. His chief complaints were difficulty in opening the mouth, dysphagia and excessive continuous production of blood and sputum-contaminated saliva.

The Departments of Dermatology and Internist medicine provided systemic therapy involving piracetam, amlodipine, doneperazil, metoclorpiramide, vitamin C, levofloxacin, dexamethasone, in addition to antiretrovirals such as lenofavir, lamivudin and efavirenz respectively.

A general examination found the patient to be alert and well-oriented. On admission, he exhibited maculopapular cutaneous eruptions on the neck, face and trunk. Extra oral examination detected the presence of sanguinolenta crusts and excessive and continuous saliva production with blood and sputum on both the upper and the lower lips. An examination for non-anemic conjunctiva and lymph node indicated no abnormalities, while ophthalmic examination revealed conjunctivitis and diffuse erythema on the upper eyelids. Intra oral examination could not be completely performed because the patient was unable to open his mouth sufficiently wide due to the pain (see Figure 1).

A laboratory examination, including a serology blood count, revealed a decline in the number of Haemoglobin 13.3 mg/dL (Normal: 14-17.6), Haematocrit 40.1% (Normal:41.5-50), MCHC 33.2% (Normal:33.4-35.5), Albumin 2.895 gr/dL (Normal:3.4-5.0), Calcium ion 5.65 mg/dL (Normal:4.7-5.2), CD4 cell count: 11 cells/µL (Normal:410-1590) and CD 4%:

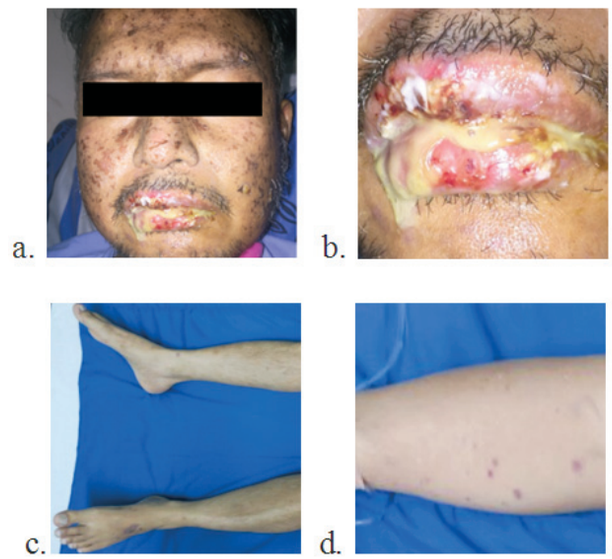

Figure 1. The first visit. a. Multiple erythematous papules and plaques were visible on the face b. Excessive and continuous production of saliva with blood and sputum was visible on the lips. c. Multiple erythematous papules and plaques were present on the lower extremities d. Multiple erythematous papules and plaques were present on the upper extremities.

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3.7% (Normal: 31-60). A serology test for HIV-1 by ELISA was positive. An Antibiotic Susceptibility Test was also performed (see Table 1) because HIV patients were often treated with antibiotics for chemoprevention of opportunistic disease and treatment of acute infection. Based on clinical symptom and laboratory evaluation, a diagnosis of oral lesions associated with multiple drug-induced SJS was made and the treatment started.

CASE MANAGEMENT

The Departments of Dermatology and Internist medicine provide systemic therapy involving piracetam, amlodipine, donepezil, metoclorpiramide, vitamin C, levofloxacin, per oral dexamethasone and antiviral drug administration using lenofavir, lamivudin and evafirenz. Patients were diagnosed with herbal medicine-induced SJS due to the occurrence of SJS after they had consumed herbal medicines composed of zingeber rhizoma, coboti rhizoma and asari epimedii herb extract. The patient was diagnosed with SJS due to having experienced myalgias, arthralgias and other flu-like symptoms after three days' consumption of the herbal medicine. The patient's symptoms worsened resulting in difficulty swallowing solid food. On his previous visits to three different hospitals he was prescribed antibiotic doxycycline, amoxicillin-clavulanic acid and paracetamol, but without any subsequent improvement. The patient was subsequently referred to the Department of Oral Medicine and diagnosed with multiple drug-induced SJS.

On his first visit to the Department of Oral Medicine, a compress with NaCl 0.9% was applied to the patient's oral cavity daily four times a day to maintain the area around the wound moist and promote the healing process. The patient was instructed to clean his teeth with a gauze moistened with NaCl 0.9% at least three times a day.

Four days later, the patient still complained of a high temperature, pain when opening his mouth, pain on swallowing, bleeding lips, sputtered saliva and spontaneous blood flow. To treat the lesion present on the lip, topical corticosteroid hydrocortisone 1% cream was applied to the affected area three times a day. After the fourth day of treatment, the patient still complained of pain in the oral cavity and lower lip on opening his mouth. A closed compress containing gauze soaked in 0.9% NaCl was applied to maintain oral hygiene, while the use of hydrocortisone 1% cream was discontinued. Chlorhexidine digluconate 0.12% spray was expected to be capable of applying the drug to the soft palate.

After nine days' treatment with Chlorhexidine digluconate 0.12% the oral lesions gradually improved as shown in Figure 2. Sanguinolenta crusts on the upper and lower lips began to reduce in size and the patient, although still experiencing pain, proved able to open his mouth.

After 18 days of treatment, the oral lesions improved as shown in Figure 3. Chlorhexidinedigluconate 0.12% spray therapy was discontinued and the patient was prescribed 5 mg of prednisone in powder form in addition to 10ml of aguadest for daily rinses three times a day for ten days and 1% hydrocortisone cream for the upper and lower lip. Saliva was diluted and the intensity of saliva secretion through

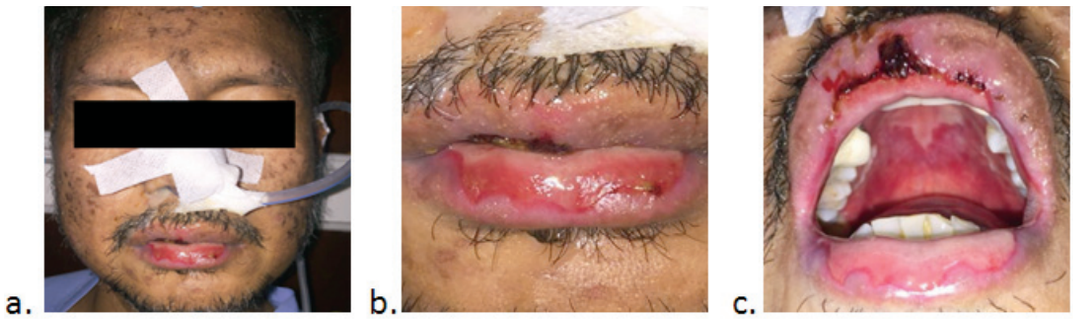

Figure 2. Oral lesions after nine days of treatment. a. Decrease in saliva around the lips. b. Hemorrhagic crusting of the vermillion zone of the lips was noted. c. Erythema of palatal mucous.

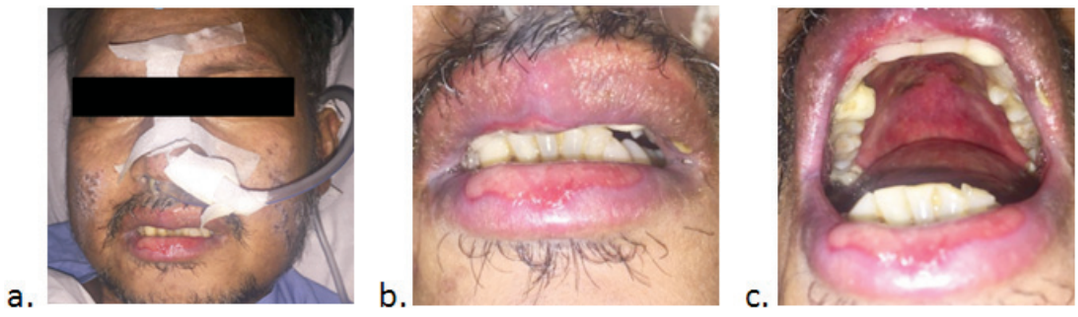

Figure 3. After 18 days of treatment lesions have improved. a. Absence of erythema on the face. b. Crusts on the lips have disappeared. c. The palatal mucous still featured an erythema.

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the lips decreased, although the patient still complained of coughing and was instructed to start a soft diet. Subsequent follow-up proved impossible as the patient died as a result of a decrease in his immunosuppressive capacity.

DISCUSSION

The patient took a mixed herbal medicine containing zingiber rhizoma, coboti rhizoma and asari epimedii herb extract. It was difficult to conclusively identify the causative ingredient that led to an allergic reaction to the patient. Epimedii extract is usually employed in kidney and asthma therapy when combined with budasonide.[22] Many patients believe herbal medicines to produce fewer side-effects and believe them to be safe. However, herbal medicines are considered to be a drug and have the potential to cause SJS.

Identifying SJS patients who have consumed suspect herbal medicine is very difficult because they will usually have injested medicine of mixed herbal composition. The subject of this research was diagnosed as suffering from SJS because he developed the condition after consuming a herbal medicine, a condition exacerbated after his being given paracetamol and amoxicillin. The precise herbal medicines that induced SJS in this patient were difficult to identify due to his having consumed a mixture containing several such medicines. Herbal medicines are often considered safe because of their natural content, whereas remedies such as guggul herbal medicine, svarnabhasma, race maniknya, ginger (zingeber officinale), gingko biloba (gingko), ginseng, St. Johns wort, godanti, echinacea purpurea, lavanabhaskar, parad preparations, Timothy grass and andrographis paniculata, among others, can cause hypersensitive reactions.[18,23,24] Studies have shown that such reactions to harmful herbal medicine often occur between the ages of 18 and 44 years. In this particular case, the patient was 43 years old. Females report a higher rate of adverse drug reactions compared to males.[18] It has been reported that the use of orally-administered herbal medicine constitute the common means of administration leading to an allergic drug reaction (36.0%). The most common allergic reactions include rash (16.2%), urticaria (15.3%), erythematosus rash (13.4%), rash (49.2%) and anaphylactic reactions (9.5%).[5]

The pathogenesis of drug hypersensitivity is not well-defined, although it is known to occur in a susceptible individual if there is exposure to a causative agent. Herbal medicines are often considered to be safer to use than chemical drugs with the result that members of the public do not take herbal drug reactions sufficiently into account. Herbal remedies contain various ingredients making it difficult to identify possible causes of the hypersensitive reaction. The SJS pathogenesis of the drug triggers an increase in the regulation of FasL produced by peripheral blood mononuclear cells. FasL will pair up with the Fas receptors in keratinocyte cells. Drug receptors trigger cells expressing MHC class 1 to produce cytotoxic CDs, Natural Killer (NK) cells and NKT cells that accumulate in epidermal blisters before secreting perforin and granzym B result in keratinocyte apoptosis.[1,6,10]

The patient had no previous history of drug allergy. A tendency to experience allergic reactions begins to occur with the appearance of symptoms of immunodeficiency disease. HIV itself can be a dangerous condition that tends to cause an immune response rather than immune tolerance.[13] Adverse cutaneous drug reactions increased as the immune system deteriorated with an apparent decrease in CD4+ T-cell count. CD4+ lymphocites constitute central regulators of the immune system that TH-1 and TH-2, which are differentiated by cytokines, release. TH-1 cells produce INF- □ and IL-2 which are important mediators within the humoral immune response, while TH-2 produces IL-4, IL-5, IL-6 and Il-10 that help B lymphocytes to produce antibodies.

HIV infection not only causes immunodeficiency, but also leads to dysregulation of the immune system. Once infected by HIV, changes in cytokines profiles appear due to an increase in production of IL-4 which is always accompanied by greater production of IL-5 and reduced production of IFN-□. In the early phase of HIV infection of the cytokines a normal balance persists. Subsequently Th-2 (IL-4) increases, while Th-1 (IL-2) decreases. Elevated serum IgE levels in HIV patients are also associated with a reduction in CD4+ cells (less than 200/mm^2). HIV, itself, causes the stimulation of B lympocytes poyclonally which, combined, finally cause an inappropriate immune response.[6,25]

Drug hypersensitivity occurs in a susceptible individual in cases of exposure to a causative agent. A delay of 4-28 days between the initiation of drug use and the onset of the adverse reaction is that regarded as most likely to support drug causality in SJS. The pathogenesis of drug hypersensitivity reactions in HIV infection is not well defined. Herbal medicines are often considered to be safer than chemical drugs with the result that herbal drug reactions are not taken into consideration by the public. Symptomatic management of the oral lesions is necessary in order to enable the patient to have oral feeds which maintain nutritional balance. SJS is a life-threatening condition and, therefore, supportive care is an essential element of the therapeutic approach.

The Departments of Dermatology and Internal Medicine provide systemic therapy involving the use of piracetam, amlodipine, donepezil, metoclorpiramide, vitamin C, levofloxacin, dexamethasone, antiviral lenofavir, lamivudin and evafirenz. Piracetam has neuroprotective and antithrombotic effects which may help to reduce death and disability.[26] Amlodipine is a first-line agent effective in improving blood pressure and patient recovery outcomes.[27] Donepezil is used to arrest the decline in cerebral blood flow, promoting preservation of functional brain activity.[28] Metoclorpiramide is used to treat the nausea and vomiting often accompanying acute migraines.[29] Vitamin C is used in the treatment of hyperpigmentation.[30] Levofloxacin produces a broad spectrum of activity against several causative bacterial pathogens of community-acquired pneumonia (CAP).[31]

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Corticosteroids may contribute to a reduced mortality rate in SJS and/or TEN without increasing secondary infection.[32] Lenofavir, Lamivudin and Evafirenz are used in antiretroviral therapy.[33]

Steven–Johnson syndrome can be induced by herbal drugs. It is essential to be aware of their potential adverse effects, especially in immunocompromised patients. Symptomatic management of oral lesions as an early intervention should be planned to decrease morbidity and mortality in SJS patients. HIV will further cause a decrease in the number of CD4+ lymphocytes and an increased IgE level. This condition can lead to herbal medicine hypersensitivity. Herbal medicines are considered safe because their natural origin is assumed to carry no risk. Certain herbal medicines can induce hypersensitive reactions producing the same effects as chemical drugs. Patients should become aware of these risks and report any serious adverse effects for the safety of others.When health care professionals construct drug histories they should actively ask their patients about all self-administered herbal medicines.

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