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**ORAL SECONDARY INFECTION IN STEVENS-JOHNSON SYNDROME PATIENT  
 WITH ORAL INVOLVEMENT: A CASE REPORT**

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**ABSTRACT**

**Background:** Stevens-Johnson syndrome (SSJ) is a hypersensitivity reaction that is often triggered by drugs but this case is rare. These reactions result in uncontrolled keratinocyte damage to the skin and mucosa throughout the body, including the oral mucosa, and are often life-threatening. The use of high doses of corticosteroids is a treatment that is often given but it can trigger secondary infections of fungal and viral in the oral cavity.

**Purpose:** This case report discusses the management of oral manifestations and secondary infections in SSJ patients, and becomes guidance for health professionals. **Case:** A 42-years-old male patient was consulted from the Department of Dermatology and Venereology (DV) due to oral pain and eating difficulties. The severity-of-illness-score for toxic-epidermal-necrolysis (SCORTEN) was 1. Erosive serosanguinous crusts, tend to bleed were found on the lips. Intraoral clinically presented wide erosive lesions and multiple ulcers, accompanied by a pseudomembranous plaque, and teeth decay. Hematologic examination showed an increase in leukocytes, neutrophil segments, monocytes, SGOT, urea, and creatinine as well as decreased hemoglobin, hematocrit, erythrocytes, MCHC, protein, and albumin. Anti-HSV1 IgG increased almost 6 times than normal values. The patient was diagnosed with SJS with oral involvement, secondary infections of pseudomembranous candidiasis, and herpetic stomatitis. **Case Management:** Systemic therapy given were intravenous dexamethasone, ranitidine, calcium, and cetirizine, from the DV Department, while hydrocortisone lip ointment, Chlorhexidine digluconate 0.12%, and Nystatin oral suspension for oral problems. The lesions progressed in 24 days. **Conclusion:** Oral secondary infections may occur in SJS patients due to high-dose corticosteroid therapy.

**Keywords:** Herpetic Stomatitis, Oral Manifestation, Oral Secondary Infection, Pseudomembranous Candidiasis, Stevens-Johnson Syndrome.

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**INTRODUCTION**

Stevens-Johnson Syndrome (SJS) is an acute life-threatening hypersensitivity reaction of mucocutaneous disease. Severe signs and symptoms present with irregular widespread lesions particularly on body, such as erythematous macules, vesicles, bullae, and purpura. The lesions involve approximately 10% of the surface area of the body and two mucous membranes or more.<sup>1-3</sup>

The etiology of SJS is unclear, but several factors that can be considered as causes include drug, allergies, infections, and idiopathy. Immunological dysregulation also mentioned as an important cause. The main mechanism of SJS is

keratinocyte apoptosis. According to WHO, about 2% of drug eruptions are classified as emergencies, because these allergic reactions require hospital treatment and may even lead to death. Some of the drugs that are considered the most common causes of hypersensitivity reactions drugs are antibiotics, anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), allopurinol, and antiretrovirals.<sup>4-5</sup>

The clinical manifestations of SJS may include an erythematous reaction on the skin with blister formation, mucosal involvement (eye, oral and genital), accompanied by fever, malaise, joint pain, and sore throat. Oral manifestations include lip ulceration and mucosa erosion. The therapy is given

as body electrolytes replacement, medication administration according to symptoms, skin protection to prevent secondary infection and fluid loss, as well as immunomodulating therapies such as glucocorticoids and immunoglobulins. Prognosis and mortality risk were assessed using the severity-of-illness score of toxic epidermal necrolysis (SCORTEN).<sup>6-8</sup>

Corticosteroids for management of SJS has been used for several years. The anti-inflammatory effect could provide healing of lesions. However, high doses and prolonged use will increase the risk of opportunistic infections, including the herpes virus and candida fungal infections.<sup>9-11</sup> This case report aims to discuss the management of oral manifestations and secondary oral infections in SJS patients so that they can serve as a guide for health professionals. Secondary oral infections found in this patient were pseudomembranous candidiasis and herpetic stomatitis.

### CASE REPORT

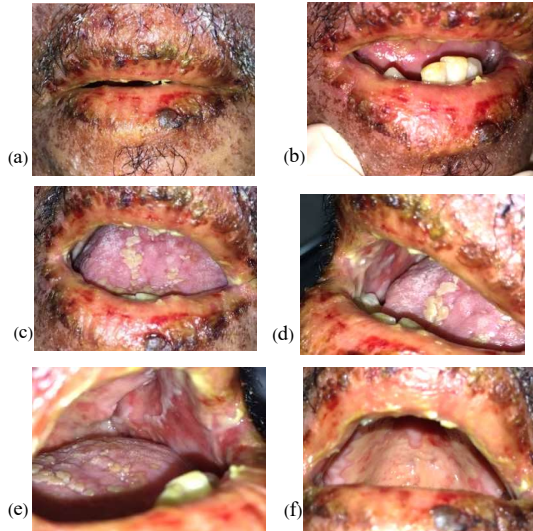
The male patient, 42 years old, was consulted to the Department of Oral Medicine, from the Department of Dermatology and Venereology, Dr. Hasan Sadikin Hospital, on the 4th hospitalization day with oral pain complaints and eating difficulties. Previous medication history was the consumption of carbamazepine for stroke therapy. Four days later, yellowish red spots appeared on the body and hands, then spread to the face and thighs, accompanied by teary eyes and blisters on the lips.

The patient appeared to be moderately ill, compos mentis, with 110/70 mmHg blood pressure, 112 times/minute heart rate, 20 times/minute respiratory rate, and 37.8 °C body temperature. SCORTEN value = 1 (from age assessment parameter > 40 years). Initial hematology test showed a decrease values for hematocrit, band neutrophils, lymphocytes, albumin, sodium, chloride, calcium, and albumin/globulin ratio; however, there was an increase in the value of leucocytes, segment neutrophils, monocytes, AST, urea, and creatinine. The 6th day hospitalization hematology test showed the decrease of hemoglobin, hematocrit, erythrocyte, MCHC, band neutrophils, lymphocytes, total protein, albumin, and albumin/globulin ratio; while monocytes, SGOT, and SGPT were increased (Table 1).

**Table 1.** Hematology test results

Examination	Day-1	Day-6	Normal value
Hemoglobin	14.0	<b>11.0 (L)</b>	14-17,4 g/dL
Hematocrit	<b>40.8 (L)</b>	<b>33.7 (L)</b>	41.5-50.4%
Eritrocyte	4.56	<b>3.63 (L)</b>	4.4-6.0 juta/uL
Leukocyte	<b>12.09 (H)</b>	7.71	4.5-11 10 <sup>3</sup> /uL
Trombocyte	290	303	150-450 ribu/uL
MCV	89.5	92.8	80-96 fL
MCH	30.7	30.3	27.5-33.2 pg
MCHC	34.3	<b>32.6 (L)</b>	33.4-35.5%
Basofil	0	0	0-1%
Eosinofil	0	0	0-4 %
Band Neutrofil	<b>0 (L)</b>	<b>0 (L)</b>	3-5 %
Segment Neutrofil	<b>75 (H)</b>	73	45-73 %
Lymphocyte	<b>14 (L)</b>	<b>17 (L)</b>	18-44 %
Monocyte	<b>11 (H)</b>	<b>10 (H)</b>	3-8 %
Blood sugar	83		< 140 mg/dL
SGOT (AST)	<b>62 (H)</b>	<b>40 (H)</b>	15-37 U/L
SGPT (ALT)	51	<b>69 (H)</b>	16-63 U/L
Total Protein	7.2	<b>5.9 (L)</b>	6.4-8.2 g/dL
Albumin	<b>2.63 (L)</b>	<b>2.3 (L)</b>	3.4-5.0 g/dL
Globulin	4.6	3.6	
Urea	<b>41.3 (H)</b>	36.0	15-39 mg/dL
Creatinin	<b>1.33 (H)</b>	0.82	0.80-1.30mg/dL
Natrium (Na)	<b>125 (L)</b>	n/a	135-145 mEq/L
Kalium (K)	3.9	n/a	3.5-5.1 mEq/L
Chloride (Cl)	<b>92 (L)</b>	n/a	98-109 mEq/L
Calsium Ion	<b>4.41 (L)</b>	n/a	4.5-5.6 mg/dL
Albumin/Globulin ratio	<b>0.57 (L)</b>	<b>0.64 (L)</b>	1.1-1.5

At the first visit (4<sup>th</sup> day of hospitalization), the patient's mouth opening appeared limited due to pain. Serosanguinolental, erosive, crusted lesions that bleed easily were seen on the patient's lips (figure 1(a), 1(b)). Intra-oral conditions appeared irregular yellowish-white plaques surrounded by erythematous edges on the tongue (1(c)), labial and buccal mucosa has erosions and extensive ulceration accompanied by white plaques between the erosive areas (figure 1(d), 1(e)), the palate mucosa showed erosive lesions and ulcers covered in yellowish-white pseudomembranes and bleed easily (figure 1 (f)). Plaque and gangrene teeth were also found, and the patient had bad oral hygiene.



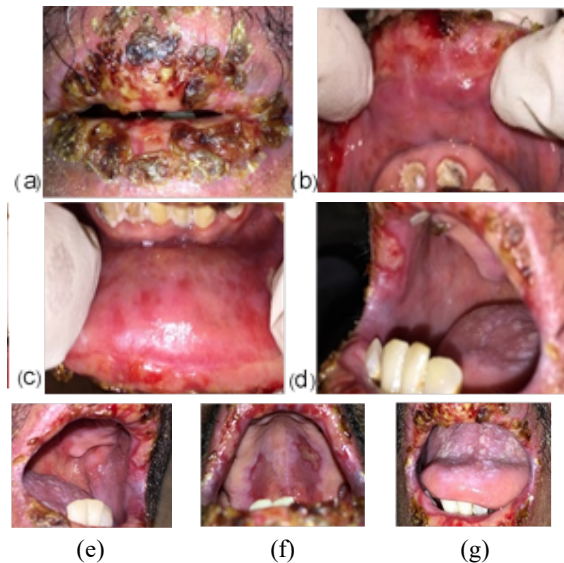
**Figure 1.** Oral conditions at first visit: serosanguinolental crust, erosive, tend to bleed on the lips (a), (b); yellowish-white plaque lesion on the tongue (c); extensive erosive and ulcerated lesions covered in white pseudomembranes on the buccal mucosa (d), (e); and palate (f).

The diagnosis in this patient was SJS with oral involvement e.c carbamazepine. In addition, the patient was also diagnosed with pseudomembranous type oral candidiasis and chronic apical periodontitis e.c 16-23, 38, 36-32, and 42 dental gangrene. The prognosis of oral mucosal involvement was good, because the patient's SCORTEN = 1, the patient was also willing to cooperate in treatments. There was a collaboration of a medical team for this patient, including oral medicine specialists (department of oral medicine/OM) and dermatology and venereology specialists (department of dermatology and venereology/DV). The patient gave verbal consent to collect documentation data for follow-up cases and scientific publications.

Therapy from the DV department was the administration of intravenous fluids with NaCl 0.9%, intravenous dexamethasone 50 mg/day (30-0-20) tapering off dose, 2x50 mg/day intravenous ranitidine, 1x10 mg/day cetirizine syrup, 2x500 mg calcium carbonate tablets once/day, and Desoximetasone cream 0.25% 2 times daily for extra oral purpura treatment. Therapy from the OM department were chlorhexidine digluconate mouthwash 0.12% 3x10 ml/day, nystatin oral suspension 100,000 IU/ml 4x2 ml/day, and 1% hydrocortisone ointment applied to the lips after compressing 0.9% NaCl 3 times a day.

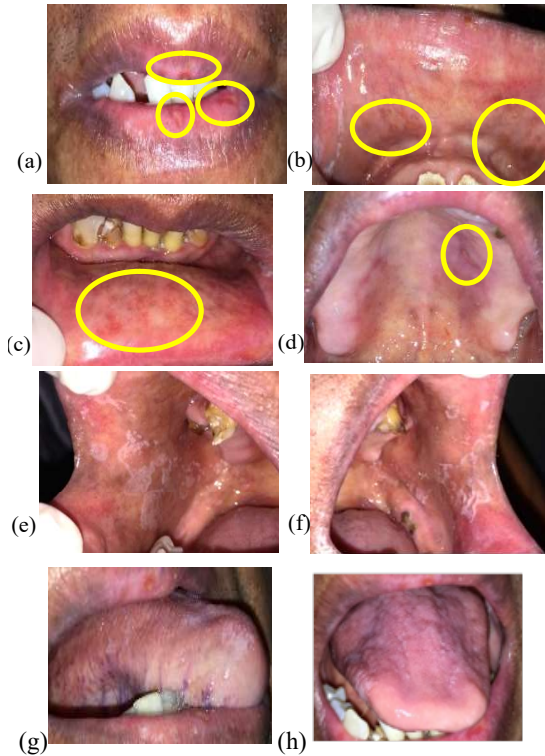
In the evaluation at the second visit after 5 days of therapy, complaints of pain in the lips was still being felt but complaints of burning in the mouth had decreased. The mouth opening was better so that the patient can eat soft foods by mouth. Erosive serosanguinous crusts were still found on

the lips, tend to bleed, and were painful (Figure 2 (a)). Intra-oral erosive lesions showed improvement compared to previous visits (figures 2(b), 2(c), 2(d)), as well as multiple ulcer lesions (figures 2(d), 2(e), 2(f)). Examination of the left buccal mucosa, dorsal tongue, and palate still showed white plaque that can be swabbed and leave the erythematous area but it has improved (2(g)), and angular cheilitis was visible at the corner of the mouth (figure 2(g)).



**Figure 2.** Oral conditions at 2<sup>nd</sup> visit: serosanguinolental crust, erosive, tend to bleed on the lips (a); erythematous macules on the labial mucosa (c), (d); ulcers on the labial mucosa (d), (e); and palate (f); White plaque lesions on the buccal mucosa, dorsal tongue and palate (g); and angular cheilitis of the mouth corners (g).

Erosive and ulcerative lesions at the previous visit were oral involvement of SJS and had improved after 5 days of therapy, whereas the ulcers seen at this second visit were suspected to be triggered by herpes simplex virus type 1, so anti-HSV1 IgG serological examination was performed. Patients planned to go home and outpatient control 1 week later. The pharmacological management of chlorhexidine digluconate mouthwash, NaCl compresses, hydrocortisone ointment, and the use of nystatin oral suspension were continued. The patient was instructed to clean the oral cavity at least 2 times a day with a soft-bristled toothbrush and gauze moistened with mouthwash for the tongue to improve oral hygiene and to eat soft-textured foods to avoid pain.



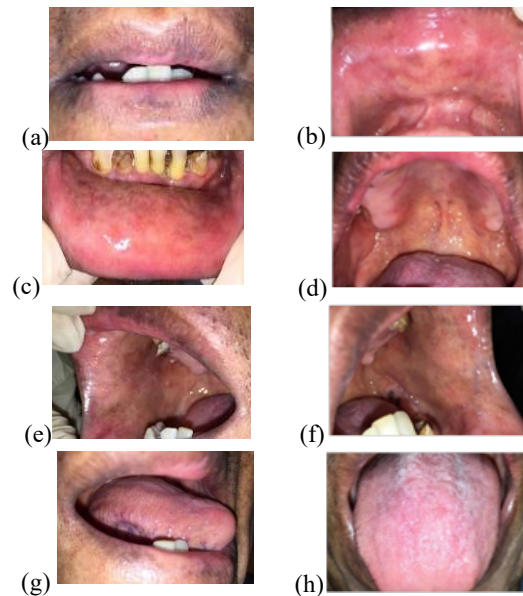
**Figure 3.** Oral conditions at the first outpatient control: there were superficial ulcer lesions with yellowish base, erythematous margins, and irregular on the lips (a), upper (b), and lower labial mucosa (c), and palate (d). There were also pseudomembranous white plaques on the right and left buccal mucosa ((e) and (f)), right lateral (g) and dorsal tongue (h), which was improved.

One week later, the patient went to the OM department for a control visit. The scabs on the body and lips had improved, but the lips were still a little sore. The results of the previously requested hematological examination showed a decrease in the hemoglobin value (11.5 g/dL) and increase in anti-HSV-1 IgG by almost 6 times the reference value (reactive = 4.58), while the normal value was under 0.8. Extraoral examination of the lips was improved and there was no more crusting, but there were multiple irregular, superficial, multiple ulcers, with yellowish base, erythematous margins, and slight pain (figure 3 (a)). Intraoral examination revealed multiple ulcers on the labial mucosa and palate showed improvement (figure 3 (b), (c), (d)). Multiple white plaque lesions on the right-left buccal mucosa, right lateral tongue, and dorsal tongue also showed improvement (figures 3 (e), (f), (g), (h)).

Based on this, the diagnosis in this patient was SJS with oral involvement (improvement), herpetic stomatitis, pseudomembranous type of oral candidiasis, and angular cheilitis (improvement). Non-pharmacological therapies were instructions for

cleaning the oral cavity with a gauze-soaked in mouthwash, especially on the tongue and cheek area, and also consume more vegetables and fruit to increase immunity. Pharmacological therapies were to continue hydrocortisone ointment for the injured lip area, chlorhexidine gluconate 0.2% 3 times a day as a mouthwash, folic acid 1 mg once a day, and vitamin B<sub>12</sub> 50 mcg twice a day.

The examination at the last visit showed that all the initial lesions had healed (figure 4 (a-g)), but there was still pseudomembranous plaque or coated tongue in the posterior 1/3 of the tongue (figure 4 (h)). The next treatment plan was to consult to the oral surgery department for extraction of residual gangrene teeth and wearing dental prostheses after the extraction. Pharmacological therapies were to continue administering folic acid and vitamin B<sub>12</sub> for the next 2 weeks.



**Figure 4.** Oral condition in second outpatient control: all lesions had healed, leaving a coated tongue in the posterior 1/3 of the dorsal tongue.

## DISCUSSION

Corticosteroid administration as the initial management of SJS with adequate doses has been used for years to provide relief and as a life-saving.<sup>7</sup> Patients in this case report received therapy from the Department of Dermatology and Venereology, in the form of a high dose steroid, namely dexamethasone 50 mg/day, divided into 30 mg in the morning, and 20 mg in the afternoon, on the first day in the emergency room. Then the dose was tapering off, adjusted according to the repair of the lesions. Based on the literature, the recommended dose of dexamethasone is 8-16 mg/day, but larger doses can be given when needed.<sup>8</sup> The duration of

corticosteroid administration is approximately 10 days,<sup>12</sup> so was this patient. Corticosteroids were chosen because they can inhibit the immunological response by suppressing interferon-gamma which triggers apoptosis and cytotoxic function of T lymphocytes.<sup>13</sup> Several factors such as tumor necrosis factor-alpha, nitric oxide, soluble Fas ligand (sFasL), granulysin, and annexin A1 are thought to cause keratinocyte apoptosis. Peripheral blood mononuclear cells (PBMCs) from SJS patients secrete soluble Fas ligand (sFasL) due to stimulation of the causative drug. Granulysin, which is produced from cytotoxic T cells or natural killer cells found in SJS skin lesions, has a concentration of two to four times higher than perforin, granzyme B, or sFasL, and decreased granulysin reduces cytotoxicity in keratinocytes. The contribution of annexin A1 in SJS keratinocyte necroptosis is that the reduction of annexin A1 by specific antibodies reduces the toxicity. Keratinocytes in the SJS release several formyl peptide receptor1, a receptor for annexin A1, resulting in increased toxicity.<sup>14</sup>

The mechanism of action of corticosteroids that suppress the immune system has a side effect of increasing susceptibility to infection.<sup>9,10,11</sup> In this case, fungal infection was Oral candidiasis and viral infection was Herpetic stomatitis. Oral candidiasis is one of the most frequent oral mucosal opportunistic infections found in patients with a suppressed immune system,<sup>11,12</sup> including patients on long-term or large doses of corticosteroid therapy. It is caused by *Candida spp.*, especially *C. Albicans*, a dimorphic fungal organism that is nonpathogenic in healthy individuals.<sup>15</sup> Oral candidiasis causes oral discomfort, pain, loss of taste sensation, and reluctance to eat. Candidiasis is mostly recognized by a clinical condition in the form of pseudomembranous white plaque. This plaque will leave an erythematous area on the base of the oral mucosa after swabbing or scraping.<sup>14,15</sup>

The viral infection was unrecognized clinically at the initial visit because the area of erosive lesions was still large. The clinical herpetic lesions began to appear at the second visit while the patient was still being treated in the hospital. Diagnosis of herpetic stomatitis was confirmed through the appearance of multiple and confluent ulcer lesions on the mucosa with a yellowish base and erythematous margins and also based on the results of laboratory tests, showing that IgG anti-HSV-1 showed reactive results.<sup>16</sup> The administration of 0.12% chlorhexidine digluconate mouthwash aims to obtain the antiviral effect of the drug in this patient. The patient was not given systemic antiviral because it was estimated that the infection has passed its acute phase. Systemic antiviral treatment will only be effective if it is given in the acute phase (6 hours to 72 hours after inoculation/reactivation of the virus).<sup>16,17</sup> Another consideration for not being given systemic antiviral was to avoid the effects of

further liver damage, which was seen from an increase in SGOT/AST values and SGPT/ALT in the patient, as well as avoiding the effects of drugs that could cause hypersensitivity reaction, such as SJS. SGOT as a biomarker of liver function, will increase due to drug metabolism in the liver and was reversible in normal condition.<sup>6,7,13</sup>

Chlorhexidine digluconate 0.12% was used as an antiseptic to prevent further infection of oral ulcers. Chlorhexidine has broad-spectrum antibacterial activity (for gram-positive, gram-negative, non-spore bacteria, fungi, and viruses). The mechanism of action is by interfering with the binding of the cationic molecule of chlorhexidine with the bacterial cell wall and by changing the osmotic balance of bacterial cells so that potassium and phosphorus leak occurs and inhibits bacterial growth. At high concentrations, it is bactericidal while at low concentrations it has a bacteriostatic effect.<sup>18</sup>

The extensive skin lesions in this patient caused dehydration, this can be seen from an increase in urea and creatinine values, as well as a decrease in protein and albumin values. The disruption of the skin continuity also causes decreased protection against foreign bodies so that the body was more susceptible to infection. The results of blood tests in this patient showed an infection process, which was seen in an increase in the value of leukocytes, segment neutrophils, and monocytes.<sup>4,5,6</sup>

The patient received folic acid 1x1 mg/day and vitamin B<sub>12</sub> 2x50 mcg/day to support the repair of oral lesions and improve anemia conditions. Anemia condition that can be seen from the results of laboratory tests in the form of decreased hemoglobin, hematocrit, erythrocyte, and MCHC values was hypovolemic anemia. It is hoped that vitamin B<sub>12</sub> and folic acid can induce erythropoiesis with systemic rehydration. Besides, vitamin B<sub>12</sub> and folic acid will form S-adenosylmethionine compounds which are involved in immune function. B<sub>12</sub> and folic acid also play a role in the regeneration and re-epithelialization of cells.<sup>19</sup>

The improvement of oral lesions has taken about 24 days. The patient stated that his oral function returned to normal after 17 days of therapy so that he could eat well which supported the speed of healing. The medical team collaboration between oral medicine specialists and dermatologists was going well so that it contributes to the healing of this patient. This is consistent with previously published case reports, that the role of oral disease specialists from the early stage is an important part of the management team for SJS patients, in reducing the morbidity of oral mucosal involvement.<sup>20</sup> Then the patient said that understood the explanations given by the medical team to avoid drugs that are likely to cause SJS.

Secondary infection may occur in Steven-Johnson's Syndrome patients with oral involvement, as a result of the administration of high doses of steroid therapy. Secondary infections found in this case were Pseudomembranous Candidiasis and Herpetic Stomatitis. The pharmacological therapy provided included administration of 0.12% chlorhexidine digluconate as antiseptic mouthwash 3x10 ml/day, nystatin oral suspension as an antifungal 100,000 IU/ml, 4x2 ml/day, and 1% hydrocortisone ointment as an anti-inflammatory, smeared on the lips after compressing 0.9% NaCl, 3 times a day. Non-pharmacological therapy was given in the form of education to improve oral hygiene, improve nutrition and hydration, and related diseases and treatment plans. Treatment for secondary infection is useful in preventing the disease from progressing more severely.

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