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CASE REPORT

Oral Complications Due to Medication in Stevens-Johnson Syndrome Patient with Systemic Involvement

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ABSTRACT

Background*: Stevens-Johnson Syndrome (SJS) is a drug-induced hypersensitivity reaction involving mucocutaneous with various trigger factors including drugs and herpes simplex virus.* ***Objective:*** *This case report aimed to discuss oral complications due to medication in SJS patients with systemic disease involvement.* ***Case:*** *A 51-year-old man was referred to the Department of Oral Medicine, Faculty of Dentistry, Padjadjaran University, at Hasan Sadikin Hospital from the dermatology and venereology department complaining of pain in the oral cavity, especially when eating and drinking two months before, with a history of phenytoin, salbutamol and theophylline therapy. Extraoral examination showed erosive lesions and tended to bleed serosanguinolenta crusts on the lips. Intraoral there were erosive lesions and white plaque on the tongue, buccal mucosa, labial mucosa, and palate, as well as dental caries and calculus. Blood examination showed low hemoglobin, hematocrit, erythrocytes, lymphocytes, monocytes, SGOT, and sodium levels, while HbA1c, random, fasting, and 2 HPP glucose levels were high. Reactive Anti-HSV-1 IgG and rheumatoid factor. KOH examination showed positive spores, hyphae, pseudohypha, and budding cells. The diagnosis was SJS-associated oral lesions with HSV-1 virus infection, oral candidiasis accompanied with diabetes mellitus. For diabetes mellitus treatment, he was referred to the internal medicine department.* ***Case Management:*** *The therapy was 0.9% NaCl for lip compress, acyclovir tablet, nystatin oral suspension, chlorhexidine digluconate 0,12% mouthwash, folic acid, and vitamin* B_{12}*. Oral lesions were improved significantly after diabetes mellitus was treated.* ***Conclusion:*** *The SJS patient was susceptible to complications in the oral cavity, especially fungal and viral infections due to the received medication.*

Keywords: *Diabetes Mellitus, Oral Lesions, Stevens-Johnson Syndrome*

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INTRODUCTION

Stevens-Johnson syndrome (SJS) is a life-threatening acute mucocutaneous disease caused by a type 4 hypersensitivity reaction.[1] The lesions involve 10% of the body's surface area and two or more mucous membranes.[2] Severe lesions present with irregular shapes on the body such as purpura, erythematous macules, bullae, and vesicles.[3] The etiology of SJS is still unknown but several predisposing factors can be considered as the cause, such as drugs, allergies, infections, and idiopathic and immune imbalances. The drugs that are thought to be the cause of hypersensitivity reactions are antibiotics, analgesics, anticonvulsants, non-steroidal anti-inflammatory drugs, allopurinol, and antiretrovirals.[4] Histopathologically the mechanism of SJS is keratinocyte apoptosis resulting in epidermal necrosis, subepidermal bullae, and inflammatory infiltrates are also seen.[5]

The clinical features of SJS are erythematous lesions on the skin along with bulla formation, involving the mucosa (eyes, mouth and genitals), fever, malaise, joint pain and sore throat. Oral manifestations are ulcerated lesions on the lips and erosion of the oral mucosa.[6] Generally, the management is to provide electrolyte fluids as a substitute for body electrolytes, skin protection to prevent secondary infection and fluid loss, as well as symptom-based drug administration and immunomodulating therapy such as immunoglobulins and glucocorticoids.[7] The prognosis was assessed using the scorten.[8]

Stevens-Johnson syndrome occurs due to a hypersensitivity reaction to drugs, one of which is Diabetes Mellitus (DM) medication.[9] Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to decreased insulin secretion, impaired insulin function, or both of them. There are two types of diabetes mellitus, diabetes mellitus type 1 (insulin-dependent) and diabetes mellitus type 2 (non-insulin-dependent). In Indonesia, the highest prevalence of DM is type 2 which reaches 90% of the total number of DM patients in Indonesia.[10] Oral manifestations that may occur in DM patients are dry mouth, periodontal disorders, gingivitis, oral candidiasis, dental caries, burning mouth syndrome (BMS), impaired taste, oral lichen planus (OLP), delayed wound healing, and increased incidence of infection.[11]

Long-term corticosteroids as the therapy for SJS patients, can cause oral complications such as herpes virus and candida infections.[12] Corticosteroids have been used for a long time to treat SJS because of their anti-inflammatory effects.[8,12] This case report aims to discuss oral complications due to medication in SJS patients with systemic involvement.

CASE REPORT

A 51-year-old male patient was referred to the Department of Oral Medicine, Faculty of Dentistry, Padjadjaran University from the Dermatology and Venereology Department, Faculty of Medicine, Padjadjaran University at Hasan Sadikin Hospital, complaining of mouth and lips sore for 2 months before. The dermatology and venereology department diagnosed the patient as SJS ec phenytoin and/or ec salbutamol and/or ec theophylline, discarded COVID-19, and grade II hypertension. History of medication was methylprednisolone, furosemide, cetirizine, ranitidine, folic acid, and vitamin B12.

Table 1. Laboratory test result

Examination	5-Apr-21	22-Apr-21	Normal Value
Hemoglobin	12,7	12,0	14-17,4g/dl
Hematocrit	39,6	35,2%	41,5-50,4%
Erythrocytes	4,6	4,21	4,5-5,9 mil/uL
Leukocytes	14,63	11,2	4,4-11,3 10^3/uL
MCH	26,3	27,6	27,5-33,2 pg
MCHC	32,1	33,7	33,4-35,5%
Rod Neutrophil	1	1	3-5%
Neutrophil segment	85	92	45-73%
Lymphocytes	11	5	18-44%
Monocytes	4	2	3-8%

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HbA1c	-	10,8	4,5-6,2%
RPG	-	558	<140mg/dL
FPG	-	191	70-100 mg/dL
OGTT	-	391	<140mg/dL
SGOT	-	62	
Protein total	-	5,9	6,4-8,2 g/dL
Albumin	-	2,63	3,4-5,0 g/dL
Ureum	-	41,3	15-39 mg/dL
Creatinin	-	1,33	0,80-1,30 mg/dL
Sodium	-	126	135-145 mEq/L
IgG anti-HSV-1	-	Reactive	
Rheumatoid factor	-	Reactive	
Candida preparation	-	Spora(+), pseudohypha(+), budding cell(+)	

Extraoral examination, tend to bleed, serosanguinolenta crusts, dry and exfoliative lower lip. There was also a white with an erythematous base ulcer, 0.2x0.8 cm in size, at the corner of the mouth. During intraoral examination there are multiple white plaques, that could be scrapped off leaving an erythematous area on the dorsum and laterals of the tongue. There were irregular, shallow, reddish base ulcers, 0.2x0.3 cm in size at the lateral and ventral tongue. Multiple white plaques at the buccal mucosa could be scrapped off leaving an erythematous area, as well as multiple, irregular, reddish base ulcers. Multiple white plaques, at the lower labial mucosa, could be scrapped off leaving an erythematous area. White plaque that could be scrapped off leaving an erythematous area at the hard palate, and shallow irregular ulcers, 0.4 cm in diameter, yellowish-white, reddish edges. Multiple white plaques at the oropharynx and soft palate. Dental examination showed caries media on tooth 25, and pulp necrosis on teeth 14,44,15,35,45,46. Plaque and calculus throughout the maxilla and mandible. The diagnosis was Suspected HAEM, suspected pseudomembranous candidiasis, angular cheilitis, traumatic ulcers at regions 35 and 46, aphthous-like ulcers of the palate, chronic apical periodontitis, and generalized chronic marginal gingivitis.

CASE MANAGEMENT

Patients were referred to the Department of Oral Medicine, Faculty of Dentistry, Padjadjaran University at Hasan Sadikin Hospital in the outpatient department after completion of inpatient treatment The management of this patient was to maintain his oral hygiene as well as communication, information, and education. The patient was instructed to brush his teeth and clean his tongue at least 2 times a day, compress the lips with 0.9% NaCl, to swish and swallow nystatin oral suspension 4 times a day @ 2 ml, gargling with 0.12% chlorhexidine digluconate mouthwash 3 times a day. Anti-HSV1 igG and KOH function tests were carried out. The KOH function test is an examination procedure to detect fungal infections in the skin or oral mucosa. This test uses the chemical compound potassium hydroxide (KOH) in its execution.

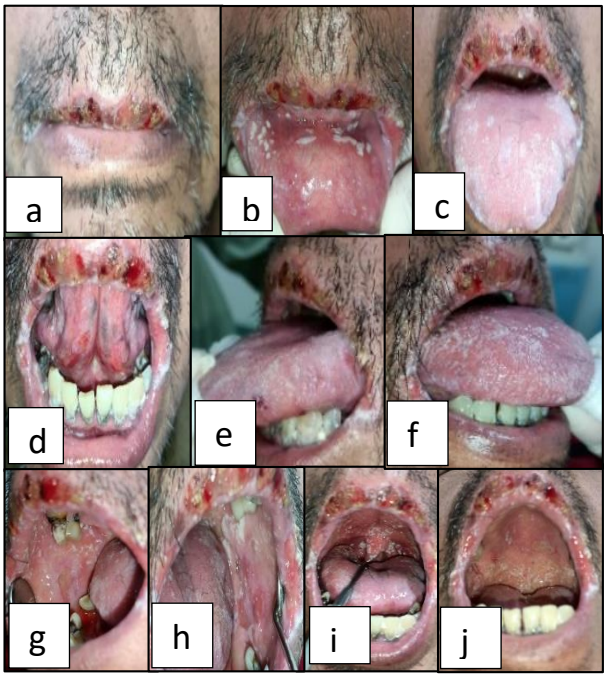

Figure 1. a, b, c, d, e, f, g, h, i and j. Extraoral: serosanguinolent crusts and ulcers at the corners of the mouth. Intraoral: multiple white plaques, which could be scrapped off leaving an erythematous area, and multiple ulcers.

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The patient is not hospitalized but instead undergoes outpatient treatment. After 2 weeks, treated with drugs at the initial visit, on the 14th-day visit, anti-HSV1 IgG was reactive, while the KOH test on the dorsum of the tongue showed spores, hyphae, pseudohypha, and budding cells. Intraorally, no improvement of the white plaque on the dorsum of the tongue (figure 2), the patient did not take nystatin regularly because he was afraid that it would run out quickly. He was instructed to take medication regularly and maintain his oral hygiene. At this visit, the management was of acyclovir tablets, folic acid, vitamin B12, nystatin oral suspension, and 0.12% chlorhexidine digluconate mouthwash. The medication was under supervision by the dermatology and venereology department due to a history of hypersensitivity reactions.

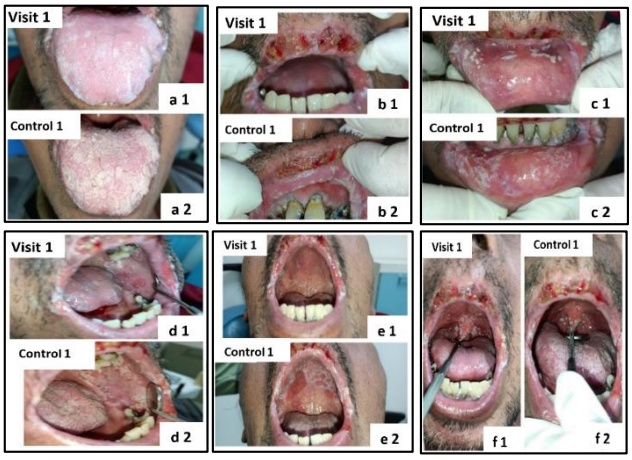

Figure 2. The clinical picture on the 1st control, pictures a1,a2, b1,b2, c1, c2, and d1, d2: white plaque was increased in the dorsum of the tongue, upper and lower labial mucosa, and buccal mucosa. Picture e1, e2, f1, and f2: white plaque was decreased in the hard palate and orofaring

On day 28th visit (2nd visit), the patient complained that the white color on the surface of the tongue was increasing. Intraoral white plaque appeared on the entire surface dorsum of the tongue, while the lesions on the right and left buccal mucosa, upper and lower labial mucosa, and the palate had not improved. The dermatology and venereology department suggested discontinuing the nystatin due to suspected hypersensitivity to nystatin, but allergy tests were not conducted due to cost constraints.

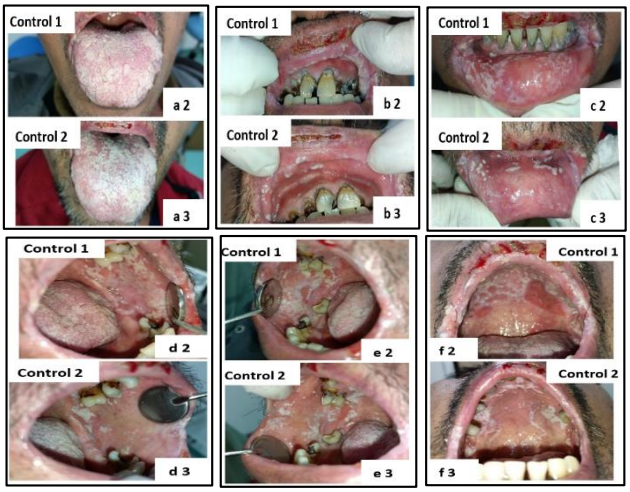

Figure 3. The clinical picture on the 2nd, the picture a2 and a3: white plaque on the dorsum surface of the tongue was increased. picture between b2 and b3, c2 and c3, d2 and d3,e2 and e3, f2 and f3: white plaque on the labial mucosa, buccal mucosa, and hard palate were decreased.

On the 42nd day visit, oral cavity complaints had greatly reduced, currently the patient was taking glibenclamide medication prescribed by internal medicine because the level of blood sugar was 558 mg/dL. The patient had discontinued nystatin. Intraoral (figure 4), the white plaque on the dorsum of the tongue was reduced and thinned. Ulcers on the buccal mucosa and palate were healed too.

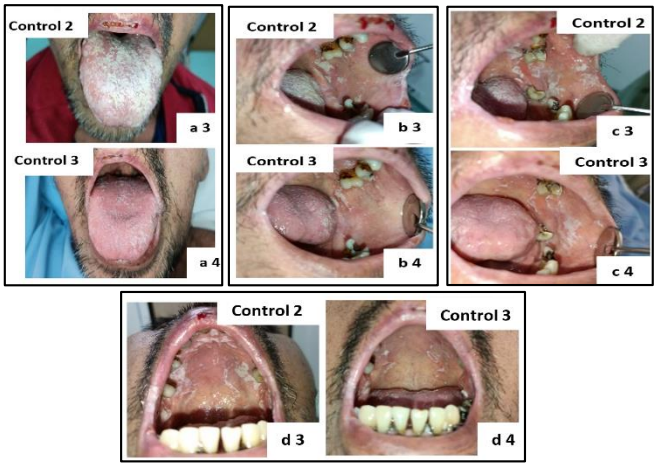

Figure 4. The picturea3 and a4, b3 and b4, c3 and c4, d3 and d4. the dorsum of the tongue, buccal mucosa and hard palate was improved.

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On the 60th day visit, there were no complaints in the oral cavity. The patient routinely took glibenclamide, cetirizine, methylprednisolone, cyclosporine, and ranitidine. Intraoral there were no lesions in the entire oral cavity (figure 5).

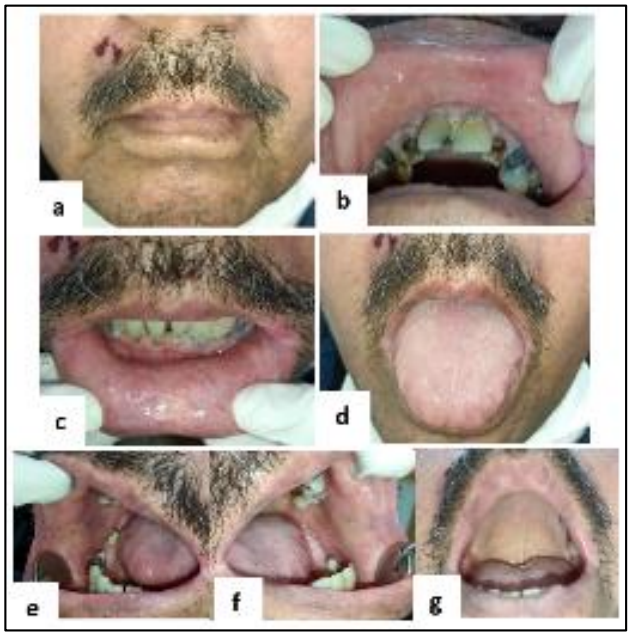

Figure 5. a, b, c, d, e, f, and g. The lesion in the patient's lips, labial mucosa, dorsum of the tongue, buccal mucosa and the hard palate was healed.

DISCUSSION

SJS is a life-threatening acute mucocutaneous disease caused by a type 4 hypersensitivity reaction. Corticosteroid is the gold standard for the management of SJS to save the patient's life.[8] The patient in this case report received therapy from the Dermatology and Venereology Department, in the form of 32 mg methyl prednisolone for 10 days and then tapered off to 16 mg. According to Kumar et al (2018), the recommended dose of corticosteroids is 8-16 mg/day, but if needed, larger doses can be given.[7] Methylprednisolone is known to reduce levels of pro-inflammatory cytokines such as interferon-gamma, TNF, and IL-6 and increase survival rates in SJS patients.[7] Corticosteroids work by suppressing the immune system so that it can cause side effects, namely the patient becomes susceptible to infection.[13] In this case the patient suffered from fungal and viral infection. Oral candidiasis is one of the most common oral mucosal complications in patients with suppressed immune systems.[12] Candidiasis is caused by Candida spp., especially C. albicans, a dimorphic fungal organism that is non-pathogenic in healthy individuals.[14] Oral candidiasis causes discomfort in the oral cavity, pain, loss of taste sensation, causing difficulty in eating, with the clinical picture of white pseudomembranous plaque, this plaque will leave an erythematous area on the base of the oral mucosa after swabbing or scrapping.[15] The patient was also infected with HSV 1 virus showed by the reactive HSV-1 IgG.

The patient's management was nystatin oral suspension, acyclovir tablets, and 0.12% chlorhexidine digluconate mouthwash. After one week of taking the medication, erosive lesions and white plaques on the dorsum of the tongue, buccal mucosa, and labial mucosa were increasing, the dermatology and venereology department recommended discontinuing nystatin oral suspension and acyclovir tablets because they suspected that the patient had a hypersensitivity reaction to both drugs, (allergy tests were not conducted due to cost constraints), but 0,12% chlorhexidine digluconate mouthwash was still continued. Chlorhexidine digluconate is an antiseptic to prevent further infection of oral lesions. Chlorhexidine has broad-spectrum antibacterial activity (for gram-positive, gram-negative, non-spore-forming bacteria, fungi, and viruses). the mechanism of action is by interfering with the binding of the cationic chlorhexidine molecule to the bacterial cell wall and altering the osmotic balance of the bacterial cell resulting in leakage of potassium and phosphorus and inhibiting the bacterial growth. At high concentrations, it is bacteriostatic, while at low concentrations it has a bactericidal effect.[16]

Extensive skin lesions in this patient led to dehydration, this could be seen from the increase in urea and creatinine values, as well as decreased protein and albumin values (Table

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1). Disruption of the continuity of the skin also causes decreasing in protection against foreign objects so that the body is more susceptible to infection. The blood examination showed increasing value of leukocytes, segment neutrophils, and monocytes, this indicated that there was an infectious process in this patient.[4] He was also treated with folic acid 1x1 mg/day and vitamin B12 2x50 mcg/day to support the improvement of oral lesions as well as the anemia. The decreased values of hemoglobin, hematocrit, erythrocytes, and MCHC showed that he was a hypovolemic anemia patient. Vitamin B12 and folic acid were expected to induce erythropoiesis by systemic rehydration. In addition, vitamin B12 and folic acid will form a compound S-adenosylmethionine which plays a role in immune function. They also play a role in cell regeneration and re-epithelialization.[17]

The improvement of oral lesions in this patient took quite a long time, about 60 days. This was due to the systemic condition of the patient who had increased blood sugar level, thus hampering the healing process, although nystatin was discontinued due to suspicion of allergy to nystatin, oral candidiasis can be cured with the use of chlorhexidine diguconate. because as is known, in addition to having an antiseptic effect, chlorhexidine also has an antifungal effect even though at a lower concentration.[18] Diabetes mellitus is a chronic disease that can reduce resistance to microbial infection and reduce the ability of tissues to repair their structure.[19] Endocrine dysfunction and metabolism involving the control of blood glucose levels leads to hyperglycemia. The patient stated that his oral function returned to normal at 60 days of therapy, after being treated for diabetes mellitus so that he could eat well which supported the healing process. Chronic hyperglycemia can trigger immunoregulatory system disorders, thereby increasing the risk of infection, due to decreased chemotaxis, phagocytosis, and microbiocidal power, including in the oral cavity such as oral candidiasis.[20] The collaboration of the medical team between oral medicine specialists, dermatologists, and internal medicine went very well so it contributed to the recovery of this patient.

CONCLUSION

Oral complications due to medication can occur in SJS patients. SJS patients are susceptible to complications in the oral cavity, especially fungal and viral infections due to the received medication. The success of oral lesion therapy in SJS patients is also influenced by the patient's systemic condition, if the systemic condition is not treated it will affect the success of oral manifestation therapy.

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