MANAGEMENT OF ORAL LESIONS ASSOCIATED WITH CARBAMAZEPINE RELATED STEVENS-JOHNSON SYNDROME / TOXIC EPIDERMAL NECROLYSIS OVERLAP PATIENT

(PENATALAKSANAAN LESI ORAL TERKAIT DENGAN PASIEN SINDROM STEVENS-JOHNSON DENGAN CARBAMAZEPINE-RELATED / NEKROLISIS RACUN EPIDERMAL YANG TUMPANG TINDIH)

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Abstract

Stevens–Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) are acute, self-limited, potentially life-threatening mucocutaneous disease. Oral mucosal involvement manifest as extensive erosions and haemorrhagic crusting, which can interfere oral functions causing odynophagia, inability to tolerate solid foods, and increased aspiration risk. A 40-year-old female patient was referred from Dermatology and Venereology department with diagnosis SJS/TEN overlap. The patient complained mouth opening difficulty due to mouth and lip sores. Drug history revealed positive intake of carbamazepine. Extraoral examination revealed multiple diffuse discrete facial lesions, conjunctival hyperemia, erosions and hemorrhagic crusting lips. Intraoral examination revealed white yellowish plaque, and erosions on buccal mucosa, palate, floor of the mouth, dorsal, ventral, and lateral tongue. Laboratory investigation revealed decrease of haemoglobin, hematocrite, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), thrombocyte, eosinophil, band of eosinophil, lymphocyte, natrium, potassium, and calcium. Oral lesions associated with SJS/TEN overlap diagnosis was made. Chlorhexidine gluconate 0,1%, nystatin oral suspension, vitamin B₁₂, folic acid, and corticosteroid ointment were given, which showed improvement of oral lesions in 3 weeks. SJS/TEN are the same disease spectrum of delayed hypersensitivity reaction leading to keratinocyte apoptosis through cytotoxic T-cell mediated Fas-Fas ligand, perforin/granzyme B, and granulysin, which distinguished primarily by severity and percentage of total body surface area involved. Currently, an optimal treatment standard for SJS/TEN patients remains unavailable. Oral lesions management play significant role in enhancing patients’ quality of life and achieving better prognosis in SJS/TEN overlap patients through multidisciplinary approach.

Keywords: Oral lesions, Stevens-Johnson syndrome, toxic epidermal necrolysis

Abstrak

diperantarai ligan Fas-Fas, perforin/ granzyme B, serta granulysin, yang dibedakan terutama berdasarkan tingkat keparahan dan keterlibatan persentase total epidermolisis permukaan kulit tubuh. Sejauh ini belum terdapat penatalaksanaan standar optimal untuk pasien SJS/ TEN. Penatalaksanaaan lesi oral berperan penting dalam meningkatkan kualitas hidup pasien dan dalam upaya memperoleh prognosis lebih baik pada pasien SJS/ TEN melalui multidisiplin ilmu.

**Kata kunci:** Lesi oral, Stevens-Johnson syndrome, toxic epidermal necrolysis

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**INTRODUCTION**

An adverse drug reactions (ADR) is defined by the World Health Organization (WHO) as a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man, while drug allergy defined as an immunologically IgE or non-IgE mediated drug hypersensitivity reaction.\(^1\) ADR is a global phenomenon which affects all ages, with implicated risk factors including drug related factors that affect its immunogenicity include its ability to act as a haptren, a prohapten or to bind covalently to immune receptors (P-i concept).\(^2\) The host related factors including increasing age and drugs intake, female appear more likely to develop drug allergies than males, concomitant disease states such as immunosuppressed patients and autoimmune disorders may predispose to the development of allergic drug reactions by altering metabolic pathways and inducing variations in the immunologic responses to drugs. The host genetic factor related with human leukocyte antigen (HLA) genotypes. It has been suggested that major histocompatibility complex (MH C) presentation of drug derived antigen plays a key role in the development of drug hypersensitivity.\(^1\)

Drug eruptions or ADR range from transient erythema to life-threatening severe cutaneous adverse reactions (SCAR) include drug-induced hypersensitivity syndrome (DiHS), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms complex (DRE SS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).\(^1,2\) SJS/ TEN represent different degrees of the same type of SCAR with high morbidity and mortality rates.\(^3\) The incidence of SJS specific ranges from 1.2 to 6 per million/ year, with fatality in 5% of cases, while TEN affects 0.4 to 1.2 per million/ year with mortality of 30% of patients.\(^4\) The incidence of SJS/TEN in South East Asia is largely undetermined.\(^5\)

SJS/TEN are acute, self-limited, rapid onset, rare but severe, potentially life threatening mucocutaneous disease clinically characterized by widespread epidermal necrosis with involvement of at least 2 mucous membranes, which predominantly triggered by ADR, rarely infections and malignancies.\(^4,6\) There are over 100 medications of various classes associated with the occurrence of SJS/ TEN.\(^4\) The high risk implicated drugs include antigout (allopurinol), antiepileptic (carbamazepine/ CBZ, phenytoin, phenobarbital, lamotrigine), antibiotic (cotrimoxazole and other sulphonamides, floroquinolone), anti-inflamatory (salasalazine), anti-HIV (nervapine), oxicamderivative nonsteroidal antiinflamatory drugs (meloxicam), and analgesic (paracetamol).\(^3,5,7\) SJS/ TEN mostly results from a cumulative effect of aligned risks related to drug structure and to the patient’s genetic predisposition (HLA alleles, drug metabolism characteristics, and T cell clonotypes),\(^3\) as well as ethnic specific.\(^5\) SJS/ TEN were historically considered part of a spectrum of erythema multiforme major, as they all present with mucosal lesions clinically similar, but these diseases are now considered apart.\(^4,8\) SJS is defined by 10% or less of total body surface area involvement while TEN is defined by 30% or greater involvement. Bodysurface involvement between 10–30% is known as SJS/ TEN overlap.\(^6\)

Oral mucosal involvement manifests as extensive erosions and haemorrhagic crusting, which can interfere oral functions causing odynophagia, inability to tolerate solid foods, and increased aspiration risk. The treatment of SJS/ TEN is multidisciplinary approach and there are still no internationally accepted management guidelines or an optimal treatment standard for SJS/ TEN.\(^3\) In this case report, we present a case of oral lesions management in SJS/ TEN overlap patient.

**CASE REPORT**

A 40-year-old female patient was referred from Dermatology and Venereology department with diagnosis SJS/ TEN overlap. The patient reported that she had chronic jaw pain for approximately 3 years since her last dental extraction. Three months before admitted to hospital, she went to her regular dentist who referred her to a neurology specialist. Two we-
Eleven weeks before admitted to hospital, the neurology specialist prescribed her CBZ. She complained of red eye, mouth opening difficulty due to mouth and lip sores, and widespread rashes on her neck, one day before admitted to hospital with preceding fever. She stated that she had no history of allergy.

Extraoral examination revealed multiple diffuse discrete facial lesions, conjunctival hyperemia, eyes and ear secrets, erosions and hemorrhagic crusting lips, and her whole body except scalp, palms, and sole of feet was covered with multiple rashes, vesicle, and epidermolysis bullae. Intraoral examination revealed white yellowish plaque, and erosions on buccal mucosa, palate, floor of the mouth, dorsal, ventral, and lateral tongue (Fig. 1).

Laboratory investigation revealed decrease of hemoglobin, hematocrite, MCV, MCH, thrombocyte, eosinophil, band of eosinophil, lymphocyte, natrium, potassium, and calcium. Oral lesions associated with SJS/TEN overlap diagnosis was made.

CASE MANAGEMENT

The patient was hospitalized for 2 weeks and within this period, regimen from dermatology and venereology department include dexamethasone 30 mg via IV, omeprazole 40 mg via IV, ibuprofen 500 mg three times daily, cendo lyteers 1 ml every one hour. We treated the oral lesions with topical corticosteroid (TC) unguent compounding of corticosteroids (dexamethasone) 0.05 mg + antihistamine (pheniramine maleate: avil) 0.5 mg + emollient base (lanolin) 2.5 g + petroleum jelly based (vaseline) 25 g three times daily, chlorhexidine gluconate 0.1% three times daily, nystatin oral suspension 2 ml four times daily, vitamin B12 50 mcg three times daily, and folic acid 1 mg once daily. All oral lesions gradually resolved in 3 weeks (Fig. 2, 3, and 4).
DISCUSSION

There was history of CBZ intake, two weeks before patient admitted to hospital. SJS/TEN is an immune disorder mostly caused by drugs, rarely infections (especially Mycoplasma pneumonia), human immunodeficiency virus (HIV), vaccinations, radiotherapy and concomitant diseases such as graft versus host disease (GVHD), lymphomas, leukemic and systemic lupus erythematosus. CBZ is an antiepileptic drugs (AED) that is effective in some people with chronic neuropathic pain, but the use of aromatic AED include CBZ, phenytoin, oxcarbazepine, phenobarbital, primidone, zonisamide, and lamotrigine is more frequently associated with drug-induced hypersensitivity reactions such as SJS/TEN.\(^5\),\(^7\),\(^10\) The highest risk of developing SJS/TEN occurs in the first 2 months of treatment with the usage of drugs on a continuous basis.\(^1\) The risk/predisposing factors of drug-induced SJS/TEN include specific HLA allele, pharmacogenetic variations in drug biotransformation or clearance, sex, hormones, drug doses or titration schedule (low dose <10 mg/day and gradual titration may allow desensitization and pharmacodynamics tolerance), and co-medication. The chemical structures of aromatic ring in AED might induce allergy via T-cell-mediated (delayed type IV) hypersensitivity reactions.\(^10\)

CBZ is one of example of the p-i concept (pharmacological interaction of drugs with immune receptors). The low molecular weight drug act as foreign antigen which binding directly and reversibly to T cells receptors (TCRs), then involved in presenting to HLA molecules of antigen-presenting cells (APCs) and provoke T cell activation. The HLA–drug–TCRs may initiate a series of immune reactions, which result in activation of CD8+ cytotoxic T cells–mediated and natural killer (NK) cell–mediated cytotoxicity. While CD8+ cytotoxic T cells and NK cells are activated, they subsequently carry out the cellular-mediated immune reactions directed at keratinocytes in an HLA class I–restricted manner. Upon activation of these responses, various cytotoxic signaling molecules or cell death mediators, including granulysin, perforin/granzyme B, and Fas/Fas ligand, and annexin A1 are relayed to the skin lesions to induce keratinocyte apoptosis. Several cytokines/chemokines involved in the pathogenesis of SJS/TEN include interleukin (IL)-2, IL-5, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, chemokine (C–C motif) receptor (CCR) 3, chemokine (C–X–C motif) receptor (CXCR) 3, CXCR4, and CCR10, which can induce cell apoptosis, activation, and differentiation, and an inflammatory response.\(^3\),\(^1\)

The patient’s complaint began with a preceding fever following with red eye, mouth opening difficulty due to mouth and lip sores, and widespread rashes on her neck, one day before admitted to hospital. The onset of signs and symptoms of SJS/TEN occurs 4 to 28 days after drug exposure, which can start, although not always, with typical or classical prodromal phase that may precede the rash by 1–2 days and lasting up to 1 week, consists of unspecified initial flu-like symptoms (malaise, fever, anorexia), sore throat, coughing, eye burning, myalgia and arthralgia. After this period, The initial skin rash, which appear suddenly and symmetrically, may be erythematous maculopapular with irregular shape or similar to a morbilliform rash, urticarial, purpuric or targetoid and is specifically tender. They usually begins on the presterol region of the trunk and rapidly spread over 3-12 days to involve the face, neck and extremities, also the palms and soles. Macular lesions become purplish or dusky red purpuric, with tendency to rapidly develop flaccid blisters that coalesced as atypical target lesions and break, resulting epidermal detachment in erythematous, oozing, raw lesions, and extensive sloughing of necrotic skin, which can easily become infected. The Nikolsky’s sign is positive in perilesional skin if mechanical pressure induces epidermal detachment, although it is not specific for SJS/TEN, as it can also be positive in autoimmune bullous skin diseases. Mucosal involvement may precede or follow the skin manifestations and occurs in two or more distinct mucosal surfaces such as ocular, ear, nose, and throat (ENT), oral, and genital lesions with clinical morphologies include erythema, enanthem, edema, and vesiculobullous that cause painful hemorrhagic erosions, coated by greyish-white pseudomembranes formations.\(^3\),\(^4\),\(^8\),\(^11\),\(^13\) Involvement of oral mucosa is seen in most of the cases with burning sensation, edema and erythema following with widespread and painful mucosal erosions or ulceraions, mostly on buccal, palatal mucosa, tongue, gingiva and lips.\(^12\),\(^13\) The extensive erosions and haemorrhagic crusting can interfere oral functions causing odynophagia, inability to tolerate solid foods, and increased aspiration risk.\(^12\),\(^15\) All the clinical manifestations of SJS/TEN overlap in our patient is concordant with the literature explained above.

There is still no universal diagnostic criteria for SJS/TEN.\(^16\) The diagnosis of SJS/TEN is based on anamnensis, clinical manifestations, and histopathological findings.\(^3\),\(^4\),\(^11\) All medications, regardless of the route of administration, must be considered, especially new drugs taken in the 8 weeks prior to the skin reaction. Assessment of the lag period (the time
between initiation of the drug and the onset of the cutaneous reaction) is 4–28 days for SJS/TEN which crucial in view of the different lag times for different cutaneous drug reactions. A comprehensive physical examination consists of prodromal phase, followed by erythema, maculopapular rash, targetoid lesions, bullae, desquamation, mucosal inflammation, and/or positive Nikolsky sign and with other systemic involvement must be assessed to get accurate diagnosis of SJS/TEN. To distinguish SJS, SJS-TEN overlap and TEN, Bastuji-Garin et al. proposed patient classification based on the body surface area percentage of skin detachment (% BSA). SJS is characterized by <10% BSA affected, SJS-TEN Overlap is between 10 and 30% BSA, and TEN is >30% BSA. Based on % BSA finding and having 2 or more mucosal membrane involvement, our patient categorized as SJS/TEN overlap. Laboratory investigation in our patient revealed decrease of haemoglobin, hematocrite, MCV, MCH, thrombocyte, eosinophil, band of eosinophil, lymphocyte, natrium, potassium, and calcium. Various laboratory abnormalities were noted in several SJS/TEN patients such as increased markers of acute inflammation. There are still no specific laboratory investigations. Furthermore, there is still inconsistency in the indication for biopsy as an inclusion criterion, with characteristic histopathology reveals keratinocyte necrosis and varying degrees of dermal-epidermal separation. Based on anamnesis, clinical examinations, and without biopsy examination, we diagnosed the case of our patient as oral lesions associated with SJS/TEN overlap.

There are still no internationally accepted management guidelines of SJS/TEN. Management of SJS/TEN involves the early identification and removal of the triggers, particularly drugs known to be high-risk, followed by multidisciplinary approach to alleviate symptoms and prevent further complications of the disease. There are several pharmacological therapies available, such as corticosteroids, intravenous immunoglobulins (IVIG), and cyclosporine. However, a universally accepted drug treatment regimen has not been established, and much controversy exists as to the role of each of these drugs individually or in combination. The role of corticosteroids in treatment of SJS/TEN is controversial because it may promote infectious complications and lead to a poorer prognosis. However, corticosteroid treatment did not increased mortality in SJS/TEN patients. The patient was hospitalized for 2 weeks and dexamethasone IV, omeprazole IV, ibuprofen, and cendo lyteers were given by dermatology and venereology specialist. Systemic corticosteroids with a high dose are considered to be able to suppress the intensity of immune reaction, control the extension of the necrotic process, decrease the injury area, reduce fever and discomfort, and prevent damage to internal organs in SJS/TEN patients at the early stage. Furthermore, a review of the highest quality evidence concluded that steroid use in patients with SJS/TEN overlap, and TEN does not reveal an increase in mortality.

We treated the oral lesions with TC, chlorhexidine mouthwash, vitamin B12, and folic acid, which resolved in 3 weeks. Mucosal hygienic maintenance are of prime importance to increase patient’s comfort, to facilitate epithelialization and to prevent complications such as infections. Specific oral care strategies can be used to minimize trauma during oral functions such as using smaller utensils and syringes. Corticosteroids play a central role in the treatment of vesiculo erosive oral lesions of autoimmune and or immunologically mediated diseases, but the evidence for the efficacy of TC in oral medicine is limited, and many of the protocols followed are drawn from experience gained in a dermatological use. Those major challenges becomes more problematic as there are very few commercial products are currently available for the topical treatment of the oral mucosal lesions. Therefore, compounded is often required. Other drugs of choice to treat erosions include chlorhexidine, octenisept or polyhexanide solutions and impregnated nonadhesive mesh gauze. Vitamin B12 and folic acid were given in order to induce erythropoiesis. Others pharmacological therapy can be delivered, if needed, such as topical lignocaine gel, antifungal agents (nystatin), others antiseptic mouthwash (e.g., bicarbonated soda, half-strength hydrogen peroxide), and topical cream to the lips (e.g., vasoline, lanolin).

Oral lesions management play significant role in enhancing patients’ quality of life and achieving better prognosis in SJS/TEN overlap patients through multidisciplinary approach. Comprehensive management of oral lesion in SJS/TEN overlap including topical corticosteroid, oral hygiene instruction, and patients’ adherence.
REFERENCES