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Case Report

Stevens-Johnson syndrome induced by carbamazepine and amitriptyline in diabetic patient: a case report

Agus Dody Pranata Suadi Putra*, Ketut Suryana, Dewi Catur Wulandari, Ida Ayu Uttari Priyadarshini

Department of Internal Medicine, Wangaya Regional Hospital, Denpasar, Bali, Indonesia

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***Correspondence:**
Dr. Agus Dody Pranata Suadi Putra,
E-mail: agusdodypranata@gmail.com

ABSTRACT

Stevens-Johnson syndrome (SJS) is systemic immune reactions (type IV hypersensitivity) that are usually present by blistering and erosions of skin and mucous membranes with involvement of multiple organ systems. The incidence of SJS is rare, with the common comorbidities are diabetes mellitus, epilepsy, hypertension, and stroke. This condition is associated with systemic proinflammatory state. Diabetes mellitus is a metabolic disorder that is characterized by abnormally elevated levels of blood glucose due to glucose intolerance, hyperglycemia, and impaired insulin secretion. Nowadays, pathogenesis of diabetes is considered to be dysregulation of immune factors that are recognized as important etiological components in the development of insulin resistance. We report a case of a 30-years-old man with fever and sore throat, who had type 2 diabetes mellitus (T2DM) and used carbamazepine and amitriptyline for diabetic neuropathy, then followed by redness and blistering on his lips, palates, face, and trunk which subsequently diagnosed with SJS.

Keywords: Steven-Johnson syndrome, Diabetes mellitus, Immune reactions

INTRODUCTION

Stevens-Johnson syndrome (SJS) is delayed-type immune reactions (type IV hypersensitivity), characterized by rapidly developing blistering and erosions of skin and mucous membranes. Mucous membranes that may be involved are in the eye, nasal, oral, genital, gastrointestinal, and lower respiratory tract.[1-3] SJS is rare but life-threatening severe cutaneous adverse reactions (SCAR). Overall, the incidence of SJS is estimated to be 1-6 cases per million people per year. In which, the incidence of SJS in the United States is 1.5-9.6 per one million population per year. Meanwhile, in China, the incidence of SJS cases is 1.8% of the hospital population and In Singapore, 0.7% cases of cutaneous adverse drug reaction are SJS. The common comorbidities are diabetes mellitus, epilepsy, hypertension, and stroke.[4]

The apoptosis of keratinocytes is the main reason for severe epidermal damage that occurs in skin and mucous membranes.[5,6] This condition is also associated with systemic proinflammatory state. Lesion that happened on SJS are induced by the migration of circulating cytotoxic T lymphocytes (CTLs) to the skin that are activated, proliferate, and release cytotoxic proteins to induce keratinocytes apoptosis.[7] Drugs are identified as the main cause of SJS cases. Carbamazepine and amitriptyline are the drugs often reported to induce severe skin symptoms, in which SJS.[8] Beside that, comorbidity of systemic disease is also identified as the condition that increases the

number of SJS cases. The most commonly occurring comorbidity among patients was diabetes mellitus.[9]

Diabetes mellitus is a metabolic disorder that is characterized by abnormally elevated levels of blood glucose due to glucose intolerance, hyperglycemia, and impaired insulin secretion. Pathogenesis of diabetes is considered to innate and adaptive immune factors that are recognized as important etiological components in the development of insulin resistance.[10] It affects abnormal proliferation of factors of the innate and adaptive immune system that observed during adipose tissue inflammation that may lead to the development of diabetes mellitus. Epigenetic genetic mechanisms controlling immune cell lineage determination, function, and migration are implicated in diabetes mellitus.[10] Here we reported a case of a patient with diabetes mellitus who developed SJS after taking carbamazepine and amitriptyline.

CASE REPORT

A 30-years-old man presented with redness and blistering on his lips, palate, face, and trunk, which started to develop 1 week before admission, followed by fever and sore throat. Patient had a history of consuming carbamazepine and amitriptyline due to diabetic neuropathy. Patient also complained of coughing, redness and swelling on both eyes. This patient had a history of type 2 diabetes mellitus, regularly used glargine and aspart for medication. There was no history of allergy to drugs before the patient was admitted.

At admission, his blood pressure was 107/70 mmHg with heart rate 130 beats/min, and temperature was 38.9°C and another vital sign was normal. On physical examination, multiple erythematous rashes, blisters, skin and mucosal detachment was found on lips, palates, face, and trunk with <18% body surface area involved (Figure 1). Redness on both conjunctiva and swollen on both eyelids was found. Laboratory tests showed leukocytosis [28.30×10^3 µl (4.0-10.00)] with high neutrophil lymphocyte ratio [18.56 (<3.13)], and high random blood glucose level [306 mg/dl (80-200)]. Based on examination, the patient was diagnosed with SJS, accompanied by diabetes mellitus and blepharoconjunctivitis. Carbamazepine and amitriptyline were discontinued due to the possible cause of drug reaction.

The patient was treated with Intravenous dexamethasone 20 mg/day, given for the 1st day, then tapered off day by day, and oral methylprednisolone was started on the 9th day of care followed by a tapered dose. Skin and mucosal lesions were cared for by topical therapy. Redness and swelling on both eyes were cared for with eye drops. Levofloxacin is given to treat leukocytosis. Glargine and aspart are continued to be used for diabetes mellitus. All medications given were tolerated during admission. Marked improvement in the skin and mucous membranes was observed progressively during treatment. Progressive clinical and laboratory improvement related to diabetes mellitus and co-morbidities also observed. Patient was discharged after 12 days of treatment with hyper-pigmented and scalded skin on lips, face and trunk.

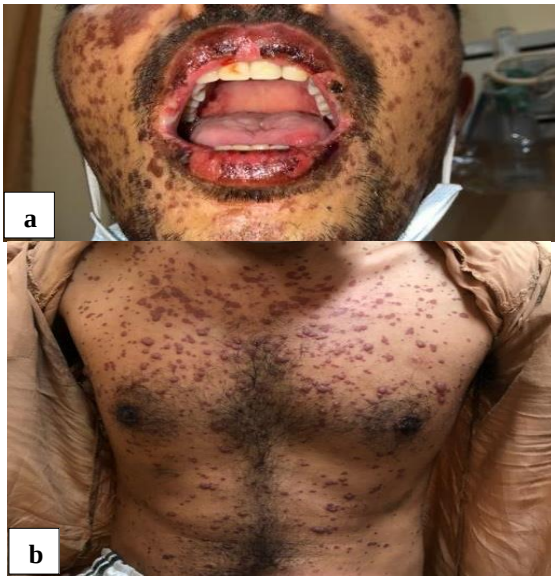

Figure 1: Erythematous, blister, skin and mucosal detachment showed in (a) lips, palates, face; (b) trunk.

DISCUSSION

In this study, we reported a case of a patient with diabetes mellitus accompanied with SJS. SJS is a spectrum of acute severe mucocutaneous adverse reaction characterized by blistering and erosions of skin and mucous membranes.[2,3] In this patient, we found redness and blistering on his lips, palate, face, and trunk. Carbamazepine and amitriptyline are used to treat neuropathy for this patient. Carbamazepine is an anticonvulsant class drugs which often reported induce SJS, while amitriptyline as a tricyclic antidepressant drug also connected to severe skin symptoms.[8] The incidence of SJS in patients with drug eruptions increases with risk factors in the form of specific alleles in the patient's human leukocyte antigen (HLA) for certain drugs. Genetic polymorphisms can determine changes in gene expression that affect the immune response, such as the HLA gene, which forms a specific type of immunological system-mediated drug eruption. A strong association was found between HLA-B 1502 and SJS caused by carbamazepine.[4]

Immune-mediated was also believed to be the pathogenesis of SJS. Widespread epidermal detachment that occurs in patients with SJS caused by the keratinocyte apoptosis and then tissue necrosis, described in histopathologic features of SJS. The current concept of specific drug hypersensitivity reaction in SJS supported also by immunological finding besides clinical and histopathological feature, in which the involvement of CTLs and natural killer (NK) cells activation.[6] Lesion that happened on SJS are induced by the migration of circulating CTLs to the skin that are activated, proliferate,

and release cytotoxic proteins to induce keratinocytes apoptosis.[7] Role of cytotoxic T lymphocyte shows in the early phase which is observed a lot of cytotoxic CD8+ T lymphocytes in the blister fluid.[8] The drug-specific CD8+ T cells activate caspase enzymes through Fas/FasL or perforin/granzyme B pathways. Apoptosis of keratinocytes is triggered, and severe epidermal damage occurs.[1] Cytokines are involved in the immune reactions of SJS. These cytokines include IFN-g, TNF-α, IL-2, IL-5, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18. These cytokines may be responsible for the trafficking, proliferation, regulation or activation of T cells and other leukocytes participating in SJS. These cytokines were found to have increased expression levels in the skin lesions, blister fluids, blister cells, peripheral mononuclear cells (PBMC) or plasma of SJS.[6]

Table 1: SJS related cytokines.[6]

Cytokines	Functions	Blister cell	Blister fluid	Skin tissue	PBMC	Serum
TNF-α	Inflammation, apoptosis	Not significant	+	+	+	
IFN- g	Activation of immune cells	+	+	+	+	
IL-2	Acute phase response, proinflammatory cytokine, anti-inflammatory cytokine	Not significant	Not significant	+	+	
IL-5				+		
IL-6	Acute phase response, proinflammatory cytokine, anti-inflammatory cytokine			+	+	+
IL-10	Anti-inflammatory cytokine	Not significant	+		+	+
IL-12	Activation of NK and CTL		Not significant			
IL-13				+		
IL-15	Regulation of T and NK cell activation and proliferation		+/-			
IL-18	Stimulation of the growth of T lymphocytes		++			

TNF-α, tumor necrosis factor-alpha; IFN-g, interferon-gamma; IL, interleukin; +, positive; -, negative

DM is a clinical syndrome associated with metabolic disorder due to impairment in insulin secretion or its action leads to hyperglycemia. Complications in diabetes are mainly caused by chronically elevated inflammatory immunity as the major cause of morbidity and mortality of diabetic patients.[11] Nowadays, the pathogenesis of T2DM is considered to be linked to both innate and adaptive immune factors that are recognized as important etiological components in the development of insulin resistance.[10] In diabetic patient, CD8+ T cells synthesized and express the pro-inflammatory cytokine IL-17, which is present in inflammatory tissues in various human inflammatory diseases. CD8+ T cells are essential for the adaptive immune response against infections by secreting cytokines, such as IFN-γ and TNF-α.

The accumulation of these cells not only induces insulin resistance, but also has a part on inflammation, apoptosis, and activation of immune cells.[6,10] Th1/Th2 ratio and levels of cytokines (e.g., IL-12, and IL-13) were also significantly elevated. IL-6 is a proinflammatory cytokine that is decisively involved in the development of insulin resistance and T2DM through the involvement of various pathways. IL-6 stimulates the production of acute-phase proteins in response to stimuli, depending on the nature or site of inflammation. The pattern of cytokine production and of the acute-phase response differs in different inflammatory conditions. Acute-phase changes reflect the presence and intensity of inflammation, and they have long been used as a clinical guide for the diagnosis and management of various inflammatory diseases, which one is SJS.[12]

Another substance which may play a role in the increased cytokine secretion is the advanced glycation end products (AGEs, which are products of glucose and lysine or arginine residues). Further, AGEs also bind to RAGE (receptor for AGEs), resulting in activation of the canonical nuclear factor κB (NF-κB) signaling pathway, which induces pro-inflammatory cytokines.[13,14] AGEs affect the biological activity of skin cells by decrease keratinocyte cell viability and migration, reduce the proliferation ability of dermal fibroblast, and induce their apoptosis.[15] From the evidence above, indicates that cytotoxic T lymphocytes and cytokines play a role as pathogenesis of SJS and diabetes mellitus. Diabetes mellitus as a comorbidity has the potential role to increase a number of cases of SJS.

We reported a case of diabetic patient who developed SJS after taking carbamazepine and amitriptyline. In diabetic patients, dysregulation of the immune system that occurs in the development of insulin resistance causes an increase of proinflammatory cytokines that result in systemic inflammatory state. On the other side, SJS causes activation on CTLs and cytokines, which also indicates systemic inflammatory state. In this case, systemic inflammatory state is indicated by elevation of neutrophil

lymphocyte ratio (NLR).[16] The first step in management of SJS is discontinue the causative agent, which in this case are carbamazepine and amitriptyline. Then, the patient was treated with intravenous corticosteroid, in this case was dexamethasone. Dexamethasone dose given was 20 mg/day for the 1st day, then tapered off day by day till 8th day. Oral methylprednisolone is started at 9th day then tapered off day by day. To prevent hyperglycemia due to steroid treatment, this patient still also received insulin treatment (glargine and aspart) and monitoring of blood sugar is performed every day in order to adjust the doses of insulin. Our case showed a progressive improvement in response to the treatment

CONCLUSION

SJS is a systemic inflammation disease that is closely related in response to the immune system. Comorbidity of systemic disease is also identified as the condition that increases the number of SJS cases. Diabetes mellitus is a metabolic disorder linked to dysregulation of the immune system that chronically elevated inflammatory immunity, as comorbidity for SJS. Cytotoxic T lymphocytes and cytokines are the part of the immune system that play as pathogenesis of both diseases. Prompt diagnosis and treatment can lead to favorable outcomes and prognosis.

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