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Case Report

Systemic lupus erythematosus patient on steroid therapy that develop to a Stevens-Johnson syndrome: a case report

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ABSTRACT

Stevens-Johnson syndrome (SJS) is a cutaneous immunity reaction involving the skin and mucosa and is an emergency condition that can be fatal. The incidence of this disease is relatively rare in the range of 1-2 per 1.000.000 population. The pathogenesis of SJS involves the immune system response of antigenic drug to body tissues but it still cannot be fully explained to date. We reported a woman, 35 years old with systemic lupus erythematosus (SLE) who had been on steroid therapy and in the course of treatment developed into SJS after administration of anti-epileptic drug. Steroids have anti-inflammatory effects mainly due to decreased syntheses or suppression of inflammatory mediators. SJS still can develop in patient with SLE who had been on steroid therapy. Giving steroid that indicated for the treatment of a disease including SLE, cannot prevent the occurrence of an allergic event including SJS. The presence of steroid can extend the duration of starting the drug with the occurrence of SJS and reduce the severity of the disease. Steroid still have a role in treatment that can be used both in SJS and SLE.

Keywords: SJS, SLE, Steroid

INTRODUCTION

Stevens-Johnson syndrome (SJS) is cutaneous immunity reaction involving skin and mucosa and it is an emergency in medicine that can be fatal. Incidence of SJS is rare about 1-2 per 1.000.000 population.[1] In Southeast Asia especially Singapore, incidence of SJS is estimated at 1.4 per 1.000.000 population.[2] Pathogenesis of SJS involves immune response to antigenic drug with body tissues which until now still cannot be fully explained.[3-5] The risk of SJS can occur up to 2 months from the start of drug administration and decrease thereafter.[1] SJS is a life-threatening disease with mortality rate of 1-5% and the mortality become higher in patients with wider skin area involvement.[1,6]

Systemic lupus erythematosus (SLE) is autoimmune disease due to formation of antibodies that cause loss of tolerance to their own bodies.[7] The SLE association in Indonesia states that the average incidence of SLE cases of 8 tertiary hospitals are 10.5% per year.[8] SLE with its various comorbidities has a 67% higher risk of death than the normal population.[8] The management of SLE with steroid is used to control the activity of the disease.[7]

Steroid is a common treatment used in inflammatory and immune reactions.[9] Giving steroid indicated for the treatment of a disease including SLE, cannot prevent the allergic reaction even SJS. The pathogenesis of SJS is still cannot fully explain to date. We reported a case of patient with SLE who was still on steroid therapy and in the course of treatment develop into SJS.

CASE REPORT

A 35-year-old female patient was complained of reddish spots on 23 August 2019. The reddish spots appeared only on the face and neck, but on 26 August 2019, complaints

of reddish spots were getting wider and spreading to the lips, neck, chest, back and upper arms of patient with peeling areas occurred on the lips of patient. Patient also felt fever that was not high and nausea. Complaints about itching, shortness of breath or any other complaints was denied by the patient.

Patient was hospitalized at Sanglah general hospital on 8 August 2019 with initial suspicion of blood disorder. Patient were confirmed diagnosed with SLE on 16 August 2019. Patient had a dyspepsia and sometimes took acid-lowering drugs. Patient often consume paracetamol and said there was no allergic reaction happened. History of drug allergies, food allergies or other allergies was denied by the patient.

Physical examination found compos mentis, BP 130/80 mmHg, HR 98 per/minute, RR 24 per/minute, tax 37.6ºC and VAS 2/10. Eye examination found erythema on palpebral and erosion covered with black crusts. Patient's lip was erythema with multiple erosion also covered with black crusts. Skin examination of the face, neck, chest, back and upper extremities found erythema and multiple papules that clearly demarcated, spread evenly with a diameter of about 0.2 to 1 cm with no bullas or crusts. Any other physical examination found no abnormality.

Laboratory examination showed leukocytes 5.94×10^3/µl, hemoglobin 9.35 g/dl, platelets 11.75×10^3/µl, reticulocytes 346.8×10^3/µl, SGOT 46.2 U/l, SGPT 152.6 U/l, albumin 3.90 g/dl, BUN 13.50 mg/dl, creatinine 0.80 mg/dl, sodium 143 mmol/l, potassium 3.64 mmol/l, uric acid 3.6 mg/dl and LDH 1.952 U/l. Coombs test was negative. ANA IF showed a titer 1:1000 with speckled pattern. IgE total examination showed a normal result 58.7 IU/ml (N<87 IU/ml).

ECG and chest X-ray examination showed no abnormalities. Head CT scan showed only left maxillary sinusitis. EEG examination showed abnormality with intermittent slow activity in the right frontotemporal region with a conclusion of moderate encephalopathy. Echocardiographic examination showed mild circumferential pericardial effusion.

Patient was diagnosed with SJS, SLE, neuropsychiatric lupus erythematosus, thrombocytopenia, mild anemia, mild pericardial effusion, dyspepsia and transaminitis.

Patient had given transfusions of PRC and TC at the initial of hospitalization. Patient had given methylprednisolone pulse dose 500 mg IV every day (16-18 August 2019) then continued with methylprednisolone 2×62.5 mg IV until the diagnosed of SJS happened on 26 August 2019. Patient was given omeprazole 2×40 mg (16-25 August 2019) and antacid 3×15 ml (16-25 August 2019).

Patient had seizures once during hospitalization (10 August 2019) and got carbamazepine 2×200 mg orally (10-23 August 2019). Patient complained of reddish spots on the face and neck since the night on 23 August 2019. The administration of carbamazepine was stopped then patient received phenytoin 3×100 mg IV (24-25 August 2019). The reddish spot getting wider with involvement in mucosa membrane of lips and eye. The administration of all drugs then stopped except steroid. Patient was diagnosed with SJS on 26 August 2019 and methylprednisolone was still continued.

Figure 1 (A-F): Lesions involving mucosa of the eyes and lips. Lesions on the face and neck, right upper arm, chest, abdomen and left upper arm patient.

The progression of SJS in skin and mucosa of patient showed improvement of efflorescence within 8 days of treatment since the SJS occurred as shown in Figure 2.

Figure 2: The progression SJS of the patient was improved within 8 days from the start of the SJS.

DISCUSSION

SJS is a life-threatening cutaneous immunity reaction involving the skin and mucosa characterized by extensive release and necrosis of epidermis.[10] SJS can be diagnosed based on history taking and physical examination.[10] Diagnosis from history taking would find a consumption of suspected drug and the time of drug administration until the manifestation of skin and mucosa occurred.[10]

In this case, the suspected drug to cause SJS was carbamazepine. In general, SJS can appear within 4-21 days after receiving a suspected drug.[4] Patient got carbamazepine (10-23 August 2019) or for 13 days then became SJS. The risk of SJS can still occur to 2 months of treatment and decreases thereafter.[1] Borelli et al stated that anti-epileptic drugs had a risk of developing SJS 8.7 times than non-epileptic drugs.[6] Based on epidemiological study from 1984 to 2013 in Southeast Asia, drugs that often cause SJS or TEN reactions (Toxic Epidermal Necrolysis) were carbamazepine (17%), allopurinol (15%), β-lactam antibiotics (13%), sulfonamide antibiotics (12%), phenytoin (9%), NSAIDs (8%) and phenobarbital (1%).[2]

Physical examinations of the skin and mucosa of the patient are similar to the efflorescence in SJS.[1,10] Laboratory investigation is not a necessity for diagnosis, but to evaluate the severity and the management of life-threatening conditions.[10] A histopathological biopsy examination of the skin is carried out if the diagnosis is doubtful.[1,10] Diagnose of SJS and TEN have the same clinical symptoms but are differentiated based on the percentage of body area involved whereas in SJS were <10% of skin involement.[1,10]

Patient was diagnosed with SLE according to the 2019 EULAR/ACR criteria with a score of 16.[7] In this case, patient had ANA titer 1: 1.000 with speckled pattern, low grade fever (score 2), seizures (score 5), pericardial effusion (score 5) and thrombocytopenia (score 4). Patient was given pulse dose methylprednisolone for 3 days then received a maintenance dose until the SJS happened. Steroids have a role in SLE management mainly due to suppression of the inflammatory mediators.[11,12]

SJS immunopathogenesis involving immune response due to antigenic drugs with body tissues.[3-5] Patients who basically have immune regulation disorders such as HIV/AIDS, malignancy or who undergo immunosuppressive therapy are more susceptible and in increasing risk of developing SJS.[1,3] Immune response as hypersensitivity due to drugs is divided into acute type if occurs <1 hour with manifestations of urticaria or anaphylaxis, and delayed type or type IV hypersensitivity occurs to a matter of hours until days after exposure to suspected allergen.[13]

Type IV hypersensitivity reactions can be mediated by T helper (Th) cells, Th1, Th2 or by cytotoxic T cells.[13] There are 4 subtype of type IV hypersensitivity reactions namely type IVa with monocytic inflammation, type IVb with eosinophilic inflammation, type IVc with cytotoxic T cells inducing keratinocyte death, and type IVd with neutrophilic inflammation.[13] In SJS, hypersensitivity reaction mainly mediated by cytotoxic T cells or type IVc with involvement of NK cells.[13] In the early phase of the disease, blister fluid of skin contains many CD8 cytotoxic T lymphocytes and shows the involvement in major histocompatibility complex (MHC) class 1.[1] CD8 lymphocytes appear dominantly in infiltrating the SJS epidermal layer. Cytotoxic T cells attack target cells by releasing granules containing cytotoxic molecules likes perforin, granzymes and granulysin or attack target cells through the expression of Fas ligand that binds to Fas in the target cell.[5,13] These results in apoptosis of keratinocytes.[1,5,13]

There are three hypotheses for the mechanism of SJS.[13] The first hypothesis is the concept of hapten pro hapten which small molecules of drug or its metabolites can activate immune reactions from T lymphocyte cells if they are covalently bound to large molecules such as peptides which then act as hapten.[3,4,13] This concept can occur in cases of chemical sensitization that causes contact dermatitis or allergies to β-lactam drugs.[13]

The second hypothesis is the pharmacological interactions concept of drug with immune receptors where drugs do not bind covalently to peptides, but bind to HLA and T lymphocyte cell receptors which stimulate directly T lymphocytes causing immune reactions.[3,13] This concept happens to carbamazepine that is found not binding to peptides.[13] In people allergic to carbamazepine, if the HLA-B*15:02 gene is found, it will increase the risk of severe allergic to SJS or TEN.[1,4,13] The same thing happens to patient with allopurinol with the gene HLA-B*58:01 will increase the risk of SJS/TEN.[1,3,13] Combination of genetic susceptibility, immune dysregulation and the addition of drug appear to play a role in SJS.

The third hypothesis is the concept of peptide changes leading to immune activation. There is a suspicion of specific drugs that bind directly to the lower part of the HLA, thereby causing a protrusion and peptide changes that cause an immune reaction by T lymphocyte cells. [3,13] This concept can occur to abacavir allergy with genetic predispositions of HLA-B*57:01 that its chemical structure can bind to the lower part of the HLA.[3,13] Based on these three concepts, peptides originating from the body itself that captured by T lymphocyte cells, will not be considered as antigens, unless the peptides or the HLA molecule changed causing identity errors as antigens. All of these concepts can cause activation of cytotoxic T lymphocyte cells which then release cytotoxic molecules and cause apoptosis of keratinocytes.[5,13]

Steroids have a role in cell immunity.[14] Steroids inhibit the activities to activate T cells by suppressing the production of pro-inflammatory mediators.[14] Naive T cells can differentiate into various T cell subtypes such as Th1, Th2,

Th17 and regulatory T cells.[14] Naive T cells which exposed to antigens can turn into helper T cells and secrete cytokines that induce the formation of cytotoxic T cells.[14] Steroids action on helper T cells may prevent the formation of cytotoxic T cells which can further prevents apoptosis of keratinocytes in the SJS due to these cytotoxic T cells.[12] SJS is a type IV hypersensitivity reaction with involvement in cytotoxic T cells and steroids appear to still have an anti-inflammatory role against T cells in immunopathogenesis of SJS.

The incidence of allergic reaction after receiving long-term steroid was also reported by Cahyadi et al which was the occurrence of SJS in SLE patient with tuberculosis.[15] In Cahyadi et al report, patient had SLE for 3 years and routinely received oral methylprednisolone but developed into SJS when tuberculosis therapy began.[15] Prolonged administration of steroid that indicated for treatment of a disease cannot prevent an allergic event. Harr et al stated that long-term use of steroid does not change the incidence or occurrence of SJS from the suspected drug.[1] The risk of developing SJS still increase from the first time the drug given and the risk will decrease after 8 weeks or more after administration of the drug.[1] Nevertheless, the presence of steroid can extend the duration of starting the drug with the occurrence of SJS as well as reduce the severity of the disease.[1]

Steroid administration is used to manage SLE and SJS. Steroid in SLE can be given to reduce systemic inflammation, maintain remission and reduce the risk of recurrence.[7] A meta-analysis and systematic review from Zimmermann et al stated that steroid still have a role in management of SJS.[16] Administration of steroid in SJS by giving prednisone dose of 1-4 mg/kg/day or methylprednisolone equivalent dose of 0.8-3.2 mg/kg/day.[7,10] Other therapies that can be used are intravenous immunoglobulin, cyclosporine, thalidomide, plasmapheresis and cyclophosphamide, but steroid and cyclosporine give better results in SJS treatment.[16] Management of SLE and SJS still uses steroid that have anti-inflammatory effects to suppress the inflammatory process according to immunopathogenesis that occurs in SLE and SJS.

CONCLUSION

We reported a 35-year-old female patient that diagnosed with SLE who received methylprednisolone and in the course of treatment developed into SJS after administration of carbamazepine. SLE and SJS disease are based on immune dysregulation and the use of steroid can suppress the inflammation that occurred. Steroid for the treatment of a disease cannot prevent the occurrence of an allergic event including SJS. The presence of steroid can extend the duration of starting the drug with the occurrence of SJS and reduce the severity of the SJS. Steroid still have a role in treatment that can be used both in SJS as well as SLE.

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