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Stevens-Johnson Syndrome induced by Piroxicam: A Case Report

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Abstract

Stevens Johnson Syndrome (SJS) is acute life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal epithelium less than 10% of the total of the total body surface area. The pathophysiology of SJS is still unclear; however, drugs are identified as the main cause of SJS in most cases. Drugs are the most important etiologic factor, >20% idiopathic or caused by infection. Many nonsteroidal anti-inflammatory drugs (NSAID) were suspected. Oxicam derivates showing the highest risk. The accurate diagnosis, avoidance of the use culprit of the drugs and rapid treatment with symptomatic and supportive care may improve the prognosis.

Keywords: Stevens-Johnson syndrome, adverse drug reaction, piroxicam

Introduction

Stevens-Johnson syndrome (SJS) is a rare life-threatening reaction, acute, and potentially fatal skin reactions involving loss of skin and, in some cases, mucosal membranes accompanied by systemic symptoms.[1] SJS is characterized by sudden apoptosis of keratinocytes leading to mucous membrane erosions and epidermal detachment. Detachment of less than 10% of the total body surface area defines SJS.[2] Some drugs that often cause of SJS are NSAIDs (45%), carbamazepine (20%), herbal medicine (13.3%), and the other drugs such as amoxicillin, cotrimoxazole, dilantin, chloroquine, and ceftriaxone.[3] Drugs are identified as the main cause of SJS in most case. NSAIDs oxicam derivatives showing the highest risk.[2] Piroxicam are medicines widely used for the relief of pain and inflammation and are commonly purchased over-the-counter in addition to being prescribed. Piroxicam is an enolic derivative of the oxicams class of NSAIDs with antiinflammatory, analgesic, antipyretic, and antiplatelet properties.[4] The pathophysiological mechanism of SJS is not fully understood. It is believed to be a delayed hypersensitivity reaction mediated by Th1 cells. SJS is traditionally thought to be a T-cell-mediated disorder. T cells are activated by binding of drugs

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to T cell receptors (TCRs) from antigen-presenting cells (APCs). Widespread apoptosis of keratinocytes is provoked by the activation of a cell-mediated cytotoxic reaction and amplified by cytokines, mainly granulysin.[2,5] Management of patients with SJS requires three measures: Early discontinuation of all medicines, particularly drugs known to be high-risk; supportive measures and active interventions.[6]

Case

A woman, 43 years old, 65 kg, came to emergency unit with a chief complaint of blisters in almost over her body since 2 days before hospitalized, accompanied by swollen eyes, sore on the lips and genital. Initially appeared itchy red spots on the chest and then spread throughout the body, then patches are partly form blister which containing clear fluid then burst and left a wound. Before appeared sore and blisters, she got prodromal symptoms like fever, malaise, sore throat, myalgia, and arthralgia, then she buys and consumed allopurinol and mefenamic acid because of sore throat, myalgia, and arthralgia. The patient had history of pain on her both legs and hyperthyroid, she had been go to the doctor, she got the therapy piroxicam, bisoprolol, and propranolol two weeks before. These medication was taken regularly every day. After receiving piroxicam for 2 weeks, the prodromal symptoms and skin lesion were appeared.

The medical history like this before was denied. There was history of hyperthyroid. No history of asthma, drug and food allergy to the patient or the family. History of applying other topical medication was denied. No history of hypertension and diabetes mellitus in patients or the family.

On physical examination, the patient's general state obtained weak, awareness compost mentis. Presented blood pressure of 110/80 mmHg, pulse rate of 90 beats per minute, respiratory rate of 18 breaths per minute, and temperature of 38,0 degrees Celsius. Based on dermatological examination on the generalize region showed erythematous macules, irregularly shaped which progressively coalescence with multiple vesicle, containing clear fluid, erosion, and there was epidermal detachment less than 10% BSA (figure 1) with a positive Nikolsky's sign. There was conjunctival hyperemia, lacrimation and discharge in both eyes. On the area of lips and oral mucous membrane were found erosions and some hemorrhagic crust, and also there was erosions on the genital area.

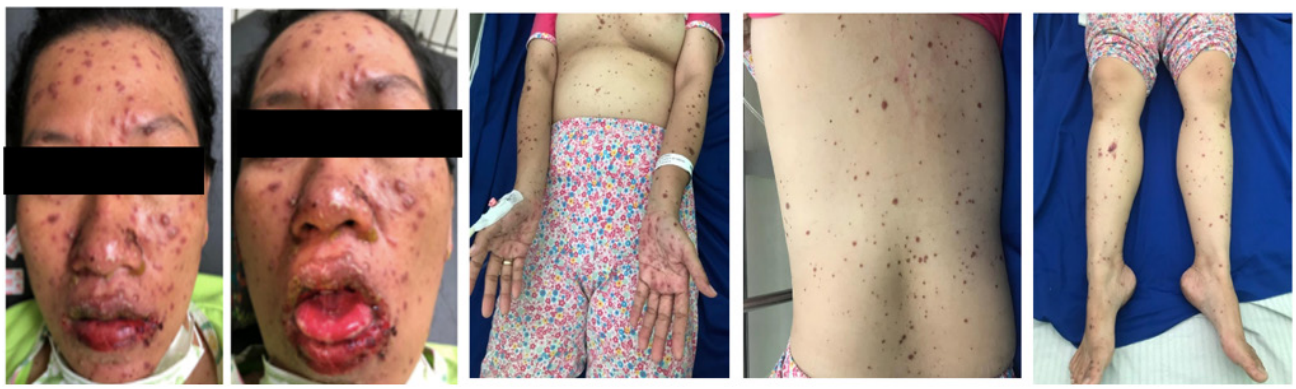

Figure 1: SJS lesions day-1.

Initial laboratory test showed the hemoglobin 12,1 g/dL (N: 11,0-14,7), total count of WBC 7,98 $x10^3/\mu L$ (N: 3,37-10,00) with normal differential count of leucocyte. From clinical chemistry examination results were abnormal: BUN 12 mg/dL (N: 10-20), albumin level 3,8 g/dL (N: 3,40-5,00), serum creatinine 0,8 mg/dL (N: 0,50-1,20), SGOT 24 U/L (N: < 41), SGPT 41 U/L (N: < 38), uric acid 5,4 mg/dL (N: < 5,7). There was slightly alteration of potassium electrolyte level 3,5 mmol/L (N: 3,8-5,0). Routine and microscopic examination of urine revealed all within normal limits. Other laboratory results from blood gas analysis HCO3 22,8 mEq/L, glucose level was 92 mg/dl, FT4 1,310 mg/dL and TSH 0,221 ulu/mL. From patient's laboratory result, has been collected several data to complete the SCORTEN scale, consist of the patient was 43 years of age, heart rate 90 beats per minute, BSA involved <10%. The level of BUN 12

mg/dL and random blood glucose were 92 mg/dL. Serum bicarbonate was 22,8 mEq/L. The SCORTEN scale of this patient was 1 with mortality rate 3,2 %.

Based on the history taking, physical and laboratory examination, the diagnosis of SJS was established. At first the five of suspected drugs was discontinued immediately. Stopping consumption of the suspected drugs were our first treatment to prevent worsen condition. Then we treat the patient with appropriate supportive treatment with IVFD triofuchsin:RD 5%:aminofluid = 1:2:1 500 cc/24hours, gentamycin injection 2x80mg iv, wound dressing with normal saline for the erosion and crusted lesion, high calori and high protein diet, and compress if fever. Initial dose of dexamethasone 0,12 mg/kg/day was given intravenously with tappered dose as the improvement of the skin lesions. After 10 days hospitalization, the skin recovery and re-epithelialization were established, temperature decreased, and mucosal complications stabilized (figure 2). There was leaving residual pigmentation on the site of skin lesions before (hyperpigmented macules). The patient was discharged after 10 days of hospitalization.

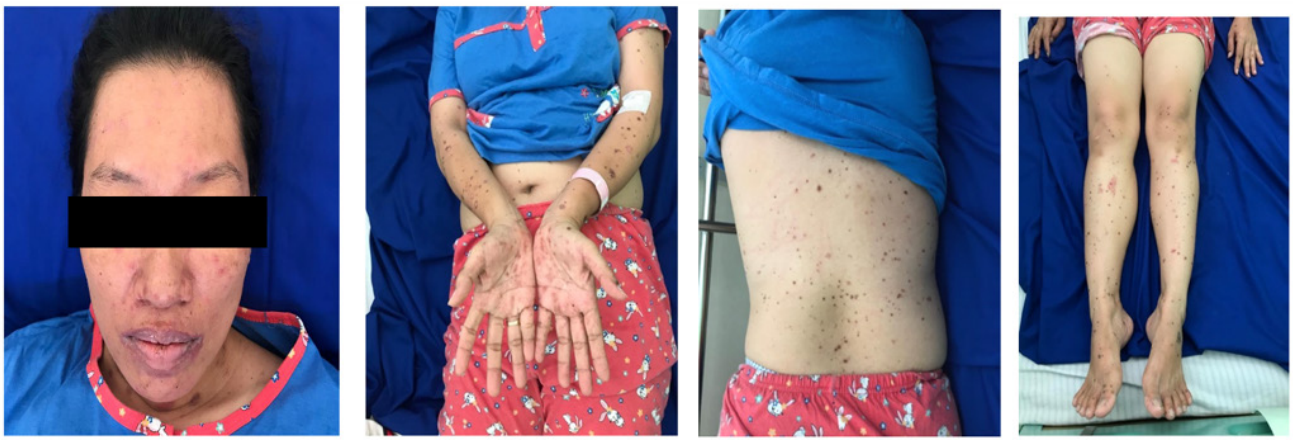

Figure 2: SJS lesions day-10.

To identify the suspected causal agent, DPT was performed 6 weeks after all the lesions completely healed. DPT using As-Is piroxicam, allopurinol, mefenamic acid, bisoprolol and allopurinol. The DPT As-Is were applied on the back and read on 48, 72, and 96 hours after applying as suggested in International Contact Dermatitis Research Group guideline (ICDRG). On 48-hour and 72-hour reading, the piroxicam patch test was positive (++), and on 96-hour reading, the piroxicam patch test was positive (+++). The patch test result of piroxicam was give crescendo tendency on 72- and 96-hour readings.

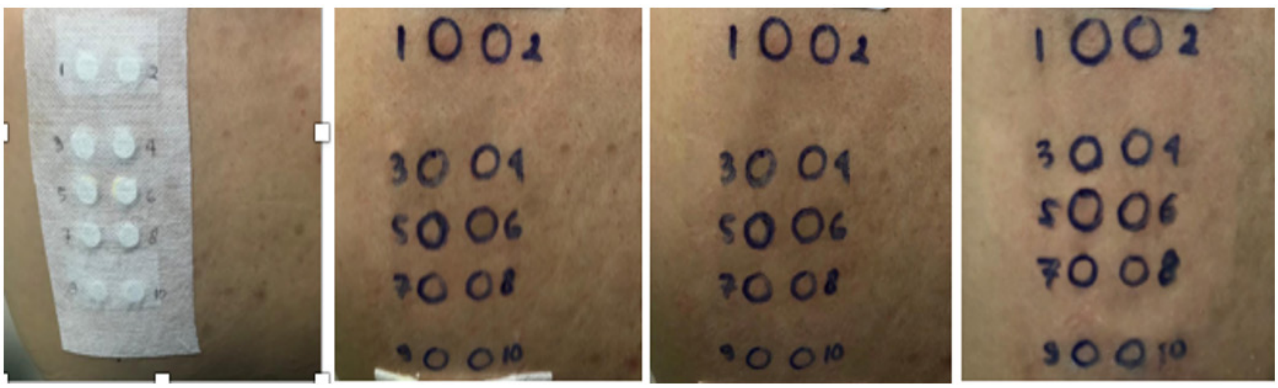

Figure 3: Drug Patch Test.

Discussion

SJS is acute life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal epithelium.[2] The diseases can start with prodromal symptoms lasting up to 1 week, such as fever, malaise, sore throat, coughing, eye burning, myalgia, and arthralgia. After the prodromal symptoms occurred may precede the mucocutaneous lesions by 1 to 3 days. Detachment of the skin, as well as mucous involvement in this case are on the eyes, oral, and genital mucosa was also observed. The eruption is initially symmetrically distributed on the face, upper trunk and proximal part of the limbs.[1,2] The initial skin lesions are characterized by erythematous, dusky red, purpuric macules, irregularly shaped, which progressively coalescence. The epidermis is detached or "detachable" (Nikolsky's sign is positive) in erythematous zones was less than 10%. SJS is characterized by involvement of <10% body surface area; SJS-TEN overlap signifies 10%–30% involvement and the most severe form of the spectrum, TEN is characterized by involvement of >30% body surface area. Mucosal inflammation (oral, ocular, and genitourinary) is nearly universal. Histopathology is usually not required for the diagnosis of SJS-TEN.[2,6]

The risk seems confined to the first 8 weeks of treatment and most inducing medications revealed the first continuous exposure between 4 and 28 days before reaction onset. The epidermal detachment progresses for 5 to 7 days. Then patients enter a plateau phase, which corresponds to progressive reepithelialization. This can take a few days to a few weeks, depending on the severity of the disease and the prior general condition of the patient. During this period, life-threatening complications such as sepsis or systemic organ failure may occur. The prognosis of the disease is determined using the score of TEN (SCORTEN). It consists of 7 parameters: Age ≥40 years, heart rate ≥120/min, presence of cancer/ hematologic malignancy, >10% body surface area involvement, raised blood urea nitrogen (>28 mg/ dL), serum bicarbonate <20 mmol/L, serum glucose level > 14 mmol/L, calculated within the first 24 h of admission of the patient. [2,6]

The immunologic pattern of early lesions suggests a cell-mediated cytotoxic reaction against keratinocytes leading to massive apoptosis. Drugs are the most important etiologic factors. The pharmacologic interaction of drugs with the immune system could result in binding of the responsible drug to MHC-1 and the T cell receptor. Most of CADR are type IV hypersensitivity reactions by Gell and Coombs, and it can be sub classified into type IVa, IVb, IVc and IVd according to the effector phenotype of the involved T cells. The pathomechanism of SJS is type IVc hypersensitivity reaction, induced by $CD4^+$ and $CD8^+$ T cells producing cytotoxic mediators (perforin and granzyme B). The epidermal damage in the skin lesions of SJS/TEN patients is considered to be of apoptotic origin. Apoptosis is induced by cytotoxic $CD8^+$ T cells through the Fas-Fas ligand (FasL) pathway or the perforin/granzyme pathway.[2,5]

Many nonsteroidal anti-inflammatory drugs (NSAIDs) were suspected to be associated with SJS. NSAIDs oxicam derivatives showing the highest risk. Piroxicam is an enolic derivative of the oxicams class of NSAIDs, inhibitor of the cyclooxygenase 1 and 2 pathway, with anti-inflammatory, analgesic, antipyretic, and antiplatelet properties. Retrospective studies implicate piroxicam in 1.6% to 12% of cutaneous adverse drug reaction cases.[2,4,7]

SJS is a life-threatening disease that requires optimal management, early recognition, and withdrawal of the offending drugs in drug-induced cases and supportive care in an appropriate hospital setting. Immediate withdrawal of all the suspected drugs is the key to the management of SJS, earlier withdrawal of the drug is associated with better prognosis.[6] Management of SJS consists of symptomatic treatment, specific treatment in acute stage, and sequele treatment. The mainstay of treatment in SJS is symptomatic and supportive care which includes fluids and electrolyte replacement, early nutritional support, control of infection, topical skin care, and eye care. Whereas specific treatment consists of corticosteroids, intravenous immunoglobulin, cyclocporine, plasmapheresis or hemodialysis, antitumor necrosis factor agents, and treatment of sequele.[2,6]

Currently, clinical diagnosis is still considered the gold standard for delayed immunologically mediated ADRs but there is consensus that in vivo testing, such as drug patch test (DPT). DPT is usually performed to the implicated drug(s) at least 4–6 weeks after delayed hypersensitivity resolution at the recommended non-irritating concentrations.[8] The basic principles and methodology for drug patch test remains same as that in patch testing for contact dermatitis. The mechanism of delayed hypersensitivity reaction in the

skin there are two phases, namely, the sensitization phase and the elicitation phase. It requires 7-10 days to develop immunological memory (sensitization phase) meaning thereby that one must have continuous exposure for this much period to the offending drug for tissue damaging hypersensitivity to develop (elicitation phase). Re-exposure to the culprit drug will elicit similar clinical reaction pattern in previously sensitized individuals.[9]

The DPT should be used as the first line of investigation or defining relevant drug in severe type of CADR including SJS. The sensitivity of DPT can vary depending on the vehicle used and the drug tested. The DPT sensitivity also varies with the type of eruption (appears most useful for generalized eczematous, maculopapular eruption, AGEP and FDE, on the other hand DPT is least useful in the investigation of SJS. Whereas the specificity of DPT have not ben yet determined.[10] The DPT is safer than other in vivo diagnostic tests to establish the diagnosis of non immediate drug hypersensitivity reactions. DPT is not invasive procedure and the lowest possibility to re-induce severe DHR, if it is compared to prick test, intradermal skin test or even drug provocation test.[9,10] Therefore, we consider performing DPT with commercially available drug (As-Is) to confirm the causative drug inducing SJS in this case, in order to prevent the second or more attack of severe CADR in this patient.

Conclusions

Stevens-Johnson Syndrome (SJS) is acute life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal epithelium. It can cause by non-steroidal anti-inflammatory drugs (NSAIDs). Oxicam derivatives showing the highest risk. The mainstay of treatment in SJS is symptomatic and supportive care which includes fluids and electrolyte replacement, early nutritional support, control of infection, topical skin care and eye care. Avoidance of use causative drug and rapid prompt treatment may improve the prognosis. Drug patch testing with positive reactions have high predictive value to avoid using causative drug in the future.

Patient Informed Consent: Proper patient consent was taken from patient for writing this case report.

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Conflicts of Interest: The authors declare no conflict of interest.

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