A PATIENT WITH DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS) AND STEVEN-JOHNSON SYNDROME (SJS) INDUCED BY DAPSONE

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KEYWORDS
Severe Cutaneous Adverse Reactions, DRESS, Steven-Johnson Syndrome, dapsone, multibacillary leprosy, septic shock, corticosteroids

Severe Cutaneous Adverse Reactions (SCAR) include Drug reactions with Eosinophilia and Systemic Symptoms (DRESS) and Steven-Johnson Syndrome (SJS) which can be fatal conditions. This report discusses the case of a 24-year-old male patient who developed DRESS and SJS after taking dapsone as part of Multi-Drug Treatment (MDT) for multibasilar leprosy (MB). The patient showed early symptoms in the form of a morphiform rash and icterus, followed by complaints of fever and weakness. Although supportive therapy and systemic corticosteroids were given, the patient's condition worsened with the appearance of lesions of the oral mucosa, bulla, and positive Nikolsky signs, indicating progression to SJS. The patient eventually died from septic shock. The report emphasizes the importance of early discontinuation of causative drugs and comprehensive supportive care in the management of complex SCAR cases.

Introduction

Severe Cutaneus Adverse Reactions (SCAR) consist of Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Steven-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN). In addition to identifying the causative drug to avoid further exposure, establishing a proper diagnosis of the type of SCAR is very important, due to different follow-up and prognosis of each type of SCAR. These syndromes have different clinical and histologic features, but sometimes the manifestations are similar that it becomes a challenge for clinicians. In some rare cases, overlapping SCARs can also occur (Casagranda, 2017).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is one of SCAR which involves skin and internal organs, and could be life threatening with a mortality rate of 10%. The incidence of DRESS is estimated to be 1 in 1000 to 10,000 drug exposures (Cho, 2017).

Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are mucocutaneus reaction characterized by the appearance of detachment of epidermis and mucosal epithelium. When mucosal involvement is <10% of body surface area, the diagnosis is SJS, but when reaches >30%, the diagnosis is TEN. SJS and TEN have a high mortality rate, varying from

10% to 50% where increasing age, significant comorbidity, and greater extent of skin detachment correlate with poorer prognosis (Mochenhaupt, 2019).

We reported a case of SCAR in a 24-year-old patient suspected due to dapsone and fulfilling the diagnostic criteria for DRESS and SJS.

Case Report

A 24-year-old man presented to the emergency ward with a chief complaint of body weakness.

The patient complained body weakness for the last 4 days. Previously, the patient was presented to the dermatology outpatient clinic with a rash over his trunk, spreading to his extremities and face. The patient complained that his eyes turned yellow and he was referred to hepatology outpatient clinic, then referred to the emergency room due to body weakness. The patient also complained of fever and stomach discomfort since 4 days before admission. Face swelling, shortness of breath, cough, nausea, and vomiting were denied.

The patient was diagnosed with multibacillary (MB) leprosy 6 weeks before admission, and had been treated with a Multi-Drug Treatment (MDT) for MB leprosy containing Rifampicin, Lamprene, and Dapsone which he took regularly. There was no previous history of food or drug allergies. History of diabetes, hypertension, heart disease, liver disease, autoimmune disease, kidney disease, were denied. History of taking other drugs was denied. The patient's occupation was a shipping company driver. Patient was married to a housewife, with no children. He had a history of free sex and tattoos.

Physical Examination

On presentation, patient was fully conscious, blood pressure 115/67 mmHg, pulse rate 96 bpm, respiratory rate 20x/min, axillary temperature 36.8^{o} C, SpO2 97% room air. Body weight was 52 kg, height 165cm, with body mass index 19,1 kg/m^2 (normal).

Physical examination revealed conjunctival pallor, scleral icterus, enlarged right posterior cervical lymph nodes and liver enlargement. Skin examination revealed morbilliform rash on his chest, back, and abdomen with indistinct borders and icteric skin underneath the lesions. On superior and inferior extremities, there were multiple erythematous macules with indistinct borders and punch out lesions on several areas. Nerve examination revealed no enlargement of the right and left auricular, ulnar, common peroneus, and posterior tibial nerves. The motoric strength of the ulnar, median, radial, and common peroneus nerve showed full motoric strength, but a slight sensory loss was found on his extremities.

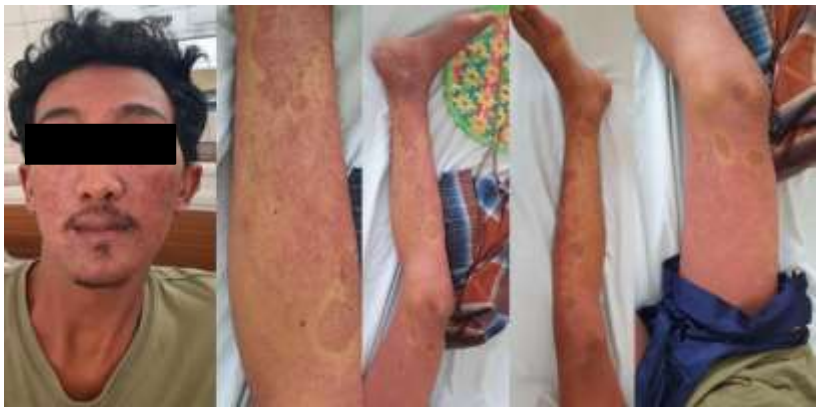

Figure 1. Morbiliform rash / multiple erythematous macules with indistinct borders, and icteric skin underneath the rash.

Initial laboratory findings showed **Hb 9.4 g/dl**, HCT 26.2%, MCV 89.1 fL, MCH 32 pg, leukocytes 12,050/uL, neutrophils 65.3%, lymphocytes 23.2%, **eosinophils 11,1%,** platelets 134,000/uL, BUN 20 mg/dl, Serum creatinine 1.15 mg/dl, albumin 3.1 g/dl, RBG 83 mg/dl, **AST 171 U/L, ALT 240 U/L, direct bilirubin 13.9, total bilirubin 21.8**, potassium 4.01 mmol/l, sodium 121 mmol/l, chloride 89 mmol/l, PPT 20.1 sec, APTT 34.2 sec, nonreactive HbsAg, non reactive anti-HCV, and non reactive anti-HIV. Peripheral blood smear confirmed normochromic normocytic erythrocyte morphology, normal leukocyte count, and thrombocytopenia. Chest X-ray showed normal heart and lung.

Patient was diagnosed with suspected dapsone-induced Drug Reaction with Eosynophilia and Systemic Symptoms (DRESS), hyperbilirubinemia, elevated liver enzyme, hypovolemic hypotonic hyponatremia, normochromic normocytic anemia, hypoalbuminemia, and multibacillary (MB) leprosy. Initial management consisted of discontinuation of the MDT for MB leprosy, normal saline infusion 1500ml/24 hours, intravenous methylprednisolone 62.5mg/24 hours, N-acetyl cysteine 600mg/ 12 hours, UDCA 500mg/ 8 hours, curcuma 20mg/ 8 hours, cetirizine 10mg/12 hours, and thiamin 50mg/24 hours, vitamin B complex 1 tablet/12 hours, and vaseline album from dermatology department. The patient was planned to be evaluated ALP, anti-HAV IgM, ANA test, and abdominal ultrasound.

Disease Course

On the third day of hospitalization, the morbilliform rash began to fade, but new vesicles appeared on the back, neck, and arms. Physical examination revealed normal vital sign. Laboratory findings showed **Hb 7.2 g/dl**, HCT 21.3%, MCV 94.7 fL, MCH 32 pg, leukocytes 13,710/uL, neutrophils 54.4%, lymphocytes 27.5%, **eosinophils 11.5%,** platelets 110,000/uL, **albumin 2.37 g/dl, AST and ALT decreased to 126 and 228 U/L**, hyponatremia was corrected to 133 mmol/l, negative IgM anti-HAV, negative ANA test, and **ALP 284** (normal 46-116). Therapy was modified to include blood transfusion until Hb ≥ 10 g/dl and intravenous albumin 20%. A skin biopsy had been performed.

On the seventh day of hospitalization, no new rash appeared, multiple vesicles on the back, neck, and arms began to dry up. Vital sign was within normal limit. Laboratory findings showed **Hb 9.7 g/dl**, HCT 28.9%, MCV 92.6 fL, MCH 31.1 pg, leukocytes 5730/uL, neutrophils 62.6%, lymphocytes 16, 8%, **eosinophils 13.8%,** platelets 170.000/uL, **albumin 2.67 g/dl, AST and ALT decreased to 67 and 172 U/L, direct and total bilirubin decreased to 13.2 and 16.9**. Abdominal ultrasound examination showed liver size ±13 cm with normal homogenous echo intensity of the parenchyme, no IHBD/EHBD widening, normal portal and hepatic vein, no nodules/cysts/mass, while the gallbladder, spleen, pancreas, kidney, prostate and bladder were within normal limits. Skin biopsy showed a focus of **basal vacuolar degeneration in epidermis, dilated capillaries with lymphocyte infiltration at dermoepidermal junction**, and no eosinophils infiltration, in accordance to an exanthematous drug eruption.

On the tenth day of hospitalization, intravenous steroid was tappered to oral methylprednisolone 16mg/8 hours. Unfortunately on the twelfth day, the patient reported mouth ulcer and blisters on his elbow. Physical examination revealed a slight rising on axillary temperature (37.6 ^{o}C), oral mucosal lesions with crusts, bullae with erythematous skin underneath and positive Nikolsky Sign. Laboratory examination showed Hb 10.9 g/dl, HCT 24.6%, MCV 90.4 fL, MCH 31.3 pg, leukocytes 7730/uL, neutrophils 77.5%, lymphocytes 14%, eosinophils 0.6%, platelets 128.000/uL, **AST and ALT decreased to 47 and 156 U/L, direct and total bilirubin were 14 and 19**. Patient's clinical examination led to a diagnosis of Steven-Johnson Syndrome. Therapy was modified to steroid tappering up to intravenous dexamethasone 5mg/8 hours, and normal saline infusion 2000ml/24 hours. The patient was consulted to ophtalmology department and was given levofloxacin eye drops/4 hours ODS and lubricant eye drops/4 hours ODS. The patient was planned for HIV test, blood & urine culture, and re-biopsy of the skin.

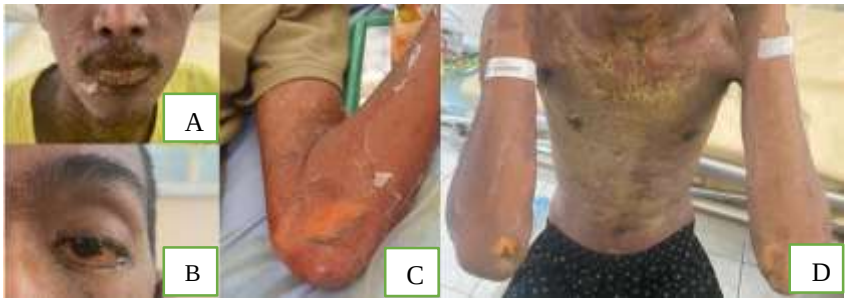

Figure 2. A, Oral mucosal lesions with crusts. **B**, hyperemia conjungtiva .**C & D,** ruptured bullae with positive *nikolsky sign*.

On the fourteenth day of hospitalization, the patient complained of body weakness and fever. Physical examination revealed blood pressure 78/50 mmHg, pulse 113 bpm, respiratory rate 22x/min, axillary temperature 37.9 ^{o}C, SpO2 97% room air. Therapy was modified to include norepinephrine pump 50 nano and intravenous ceftriaxon 1g /12 hours. HIV test was non-reactive, while blood cultures, urine cultures, and re-biopsy of the skin were still waiting for the results.

On the sixteenth day of hospitalization, the patient experienced a decrease of consciousness. Physical examination revealed GCS 345, blood pressure 90/52 mmHg with 100

nano norepinephrine pump, pulse 120 bpm, respiratory rate 24x/min, axillary temperature 38.4 ^{o}C, SpO2 97% with 6 lpm simple mask. The patient unfortunately passed away on the seventeenth day due to septic shock. The results of urine culture showed *Eschericia coli* ESBL, while blood culture showed no growth of bacteria. The re-biopsy of the skin showed a detached epidermis forming a subepidermal blister, lymphocyte and neutrophil infiltration with foamy macrophages and 1-2 acid-fast bacilli (AFB) at the dermoepidermal junction.

Discussion

Cutaneous adverse drug reaction are a common public health problem, affecting about 10% of hospitalized and 1-3% patients with multi medication. But, 2% of cutaneous adverse drug reaction are characterized as severe reactions that require hospitalization, known as Severe Cutaneous Adverse Reaction (SCAR) (Formica, 2018). Severe Cutaneus Adverse Reactions (SCAR) consist of Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Steven-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN). However, the presentation of SCAR can be ambiguous, which will be challenging for clinicians. In some cases, overlapping SCARs can also occur (Casagranda, 2017).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a complex and potentially life-threatening drug hypersensitivity reaction, characterized by skin eruptions, haematological abnormalities (eosinophilia, atypical lymphocytes), lymphadenopathy, and involvement of organs such as liver or kidneys.

In this case, the patient was presented with icterus, right posterior cervical lymph nodes enlargement, and skin eruption in the form of morbilliform rash with indistinct borders that spread throughout the body. Laboratory findings showed eosinophilia, elevated liver enzymes, and hyperbilirubinemia.

The global prevalence of DRESS was 2.18 to 9.63 cases per 100,000 patients in 2016 (Hiransuthikul, 2016). The most common patient's comorbidities were HIV (28.8%), atopy (21.9%), and epilepsy (20%). Drugs suspected in DRESS include anticonvulsants, allopurinol, sulfonamides, and antibiotics. In average, the onset of DRESS is 2-8 weeks after ingestion of the suspected drug.

In this case, the patient was presented with sign and symptomps of DRESS after taking MDT for MB leprosy containing Rifampicin, Lamprene and Dapsone for 6 weeks. The culprit drug in this case is dapsone, because dapsone/diaminodiphenyl sulfone (DDS) belongs to sulfonamide antibiotics which are included in highly suspected drugs causing SCARs

Several retrospective studies reported DRESS mortality rate of 3.8% to 10% which is often due to organ failure, shock, and sepsis. Skin histopathology in DRESS is highly variable and non pathognomonic, but skin biopsy is still recommended to exclude other causes that have pathognomonic histopathology. Histopathology which can be found in DRESS include lymphocytic infiltrates, hyperkeratosis, dyskeratosis, lymphocytic exocytosis, and spongiosis. Eosinophils in the dermis and dilated capillaries are not always found (Cabanas et al, 2020).

In this case, skin biopsy on the fourth day of hospitalization showed a focus of basal cell vacuolar degeneration in epidermis, dilated capillaries with lymphocyte infiltration at the dermoepidermal junction, and no eosinophils infiltration. The result of skin biopsy was in accordance to exanthematous drug eruption.

RegiSCAR established a scoring system using clinical, biological, and histological parameters to classify SCARs as "definite", "probable", "possible", or "excluded". Currently the available RegiSCAR scoring system can be used to establish the diagnosis of AGEP and DRESS, while the diagnosis for SJS and TEN can be established by clinical examination. Two SCARs can be considered as an overlap if the case can be classified as "definite" or "probable" for two SCARs (Casagranda, 2017).

In this case, the presence of fever, enlarged lymph nodes, eosinophilia, skin involvement and liver involvement supports the diagnosis of "definite" DRESS with a total score 6 based on the RegiSCAR score which can be seen in table 1.

Table 1. RegiSCAR scoring for DRESS

Score	-1	0	1	2	Min.	Max.
Fever ≥38,5° C	No/Unknown	Yes			-1	0
Enlarged lymph node		No/Unknown	Yes		0	1
Eosinophylia		No/Unknown			0	2
Eosinophyl (x 10^9/l)			0.7-1.499	≥1.5		
Eosinophyl, if leukocyte <4.0x10^9 /l			10-19.9%	≥20%		
Atipical lymphocyte		No/Unknown	Yes		0	1
Skin involvement					-2	2
Skin rash extent (% body surface area)		No	>50%			
Skin rash suggesting DRESS	No					
Biopsy suggesting DRESS	No	Yes/Unknown				
Organ involvement					0	2
Liver			Yes			
Kidney		No/Unknown	Yes			
Lung		No/Unknown	Yes			
Muscle/heart		No/Unknown	Yes			
Pancreas		No/Unknown	Yes			
Other organ		No/Unknown	Yes			
Resolution ≥15 days	No/Unknown	Yes			-1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/Mycoplasma						
If none positive and ≥3 above negative			Yes		0	1
Total Score					-4	9
Note : score <2 excluded, 2-3 possible, 4-5 probable, >5 definite						

Steven-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) is a severe drug hypersensitivity reaction, characterized by skin eruption, epidermolysis, mucosal involvement,

and systemic symptoms. A diagnosis of SJS is established if the epidermal involvement is <10% body surface area, and TEN if the epidermal involvement is >30%.

In this case, On the twelfth day of hospitalization, the patient presented with fever, oral and lip mucosal lesions with crusts, bullae with an erythematous skin base and a positive nikolsky sign.

Although the diagnosis of SJS can be made clinically, histopathology from skin biopsy is necessary to support the diagnosis and exclude other skin diseases such as erythema multiforme, pemphigus vulgaris, bullous pemphigoid, and other bullous diseases. Histopathology that can be found in SJS/TEN is various degree of epidermal damage, perivascular lymphocytic infiltrates which can be accompanied by eosinophils in the dermis, and skin adnexal damage such as sweat glands and hair (Creamer, 2018).

Re-biopsy of the skin was performed and showed detached epidermis forming a subepidermal blister, lymphocyte and neutrophil infiltration at the dermoepidermal junction with foamy macrophages and 1-2 acid-fast bacilli (AFB). The acid-fast bacili found in the skin biopsy was reffered to leprosy, while the detached epidermis and lymphocyte infiltration was in accordance to SJS.

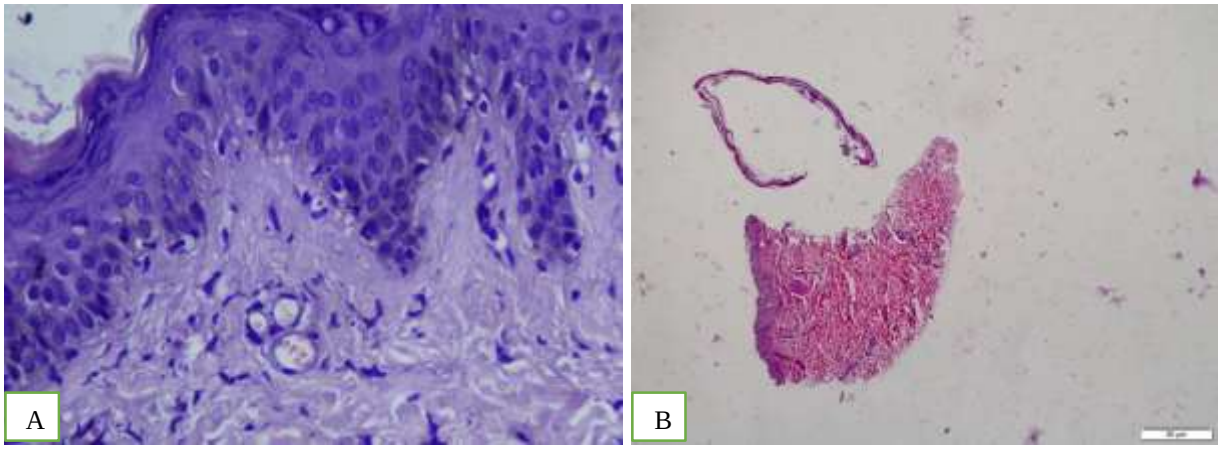

Figure 3. A, First skin biopsy on day-3 showed vacuolar basal cell degeneration in the epidermis, and dilated capillary with lymphocyte infiltration at dermoepidermal junction. **B**, Second skin biopsy on day-10 showed detached epidermis forming subepidermal blister.

The initial management of a patient diagnosed with DRESS is discontinuation of all suspected drugs. The prognosis is better if the causative drug is stopped early. The next treatment is hospitalization, systemic corticosteroids in severe cases, fluid and electrolyte therapy, nutritional therapy, and supportive therapy including antipyretics such as acetaminophen, antihistamines such as first and second generation of H1-antihistamines, topical skin care such as emollients and dressing, as well as laboratory monitoring of the organs involved and multidisciplinary work up consisted of dermatologist and allergist. Acetaminophen can be used safely as an antipyretic despite the presence of liver injury in DRESS because it has been studied in variety of liver disease without evidence of increased risk of hepatotoxicity at currently recommended dose (Yan, 2018). Second generation of H1-antihistamines such as cetirizine, loratadine, levocetirizine, and

desloratadin are preferred than the first generation due to its more rapid onset and long term effects, no effects on serotonin and acetylcholine receptors, and its additional antiallergic effects such as stabilize the mast cell membrane, reduce the production of adhesion molecules (ICAM-1), and suppress eosinophil-induced release of IL-8 (Yanai, 2017). Empirical antibiotics and NSAIDs are avoided in DRESS (Cabanas, 2020). Corticosteroids that can be given are methylprednisolone 1-2 mg/kgBW/day. In the presence of liver injury, curcumin has a decent evidence as a hepatoprotective agent. In several studies, curcumin improved the deficiency of antioxidants levels, and it induces the survival of hepatocytes (Karamalakova, 2019).

In this patient, MDT for MB leprosy was discontinued after the patient experience sign and symptoms suggestive of DRESS. Therapy for this patient included intravenous normal saline 1500 ml/24 hours, intravenous methylprednisolone 62.5mg/24 hours, UDCA 500mg / 8 hours, curcuma 20mg / 8 hours, cetirizine 10mg / 12 hours, and thiamin 50mg / 8 hours, vitamin B complex 1 tablet /12 hours, vaseline album from dermatology department. Antibiotics and NSAID were not administered. The steroid was administered for ten days and after the clinical condition was well improved, intravenous methylprednisolone was tappered down to oral methylprednisolone 16mg / 8 hours. On the twelfth day, unfortunately patient reported fever, red eyes, and oral lesions. Physical examination revelaed oral mucosal lesions with crusts, and bullae with an erythematous skin base with skin involvement <10%, and a positive Nikolsky sign leading to a diagnosis of Steven-Johnson Syndrome.

Initial treatment for SJS patients is discontinuation of all suspected drugs, followed by supportive therapy including patient placement in specific unit (burn unit or intensive care unit), fluid and electrolyte replacement therapy, nutritional therapy, skin care, eye care, oral care with antifungal agents or antiseptic, and systemic corticosteroids. Blood cultures, urine, and skin biopsies are also recommended (Mockenhaupt, 2019). Although the use of corticosteroid in Steven-Johnson Syndrome is controversial due to increasing risk of infection, some studies stated that the general negative opinion of corticosteroid is probably because they are often given too late, in too low dose, and for too long duration. Therefore, short courses of high dose corticosteroid in early SJS have a good rationale. Dexamethasone is a high-potency glucocorticoid with pleomorphic effects on the immune system and may inhibit epidermal apoptosis by several mechanisms including inhibition of T-cell activated apoptosis by suppression of various cytokines such as TNF alpha, so that a short-term injection of Dexamethasone 0.15-0.2mg/kgBW/day may be considered in SJS therapy (Law, 2015). Fluid replacement therapy can be estimated with the formula 2 ml/kgBW/% body surface area. Nutritional therapy can be met at 20-25 kcal/kg in the catabolic phase, and nutrition via a nasogastric tube is considered if the patient has multiple oral lesions. Skin care is performed by irrigating the lesions regularly with sterile water, emollients, and antimicrobial dressing on lesions with necrotic tissue. Eye care can be performed by giving lubricants and also antimicrobials and steroid eye drop. Antibiotics are only given if there are clinical signs of bacterial infection (Creamer, 2016).

The patient was given intravenous fluid therapy of normal saline 2000ml/24 hours and tappering up of oral steroid to intravenous dexamethasone 5mg/ 8 hours. The dermatologist gave

vaseline album as emollient, sodium fusidate ointment for skin lesions, and irrigation of the lesions with normal saline. The ophtalmologist gave levofloxacin eye drops and lubricant eye drops. Then on day-14, intravenous ceftriaxon 1g/ 12 hours was administered because the patient showed clinical signs of bacterial infection, while waiting for the results of blood and urine cultures.

In severe DRESS, systemic steroids are highly recommended. Methylprednisolone 60-120mg per day or other equivalent steroids are suggested, with a tappered dose of 5-10mg weekly. Another important thing is that the suspected drug in this case, dapsone, can last for 35 days in the body so it is necessary to tapp off slowly for up to 4-6 weeks. Meanwhile in SJS, steroid administration is controversial because although it is suitable with the pathogenesis of SJS which is a type four allergic reaction, it is mentioned in some studies that it can increase mortality due to infection, so a potent steroids are recommended only in a short term such as Dexamethasone 0.15-0.2 mg/kgBW/day (Creamer, 2016).

Conclusion

We reported a case of a patient with dapsone-induced Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) and Steven-Johnson Syndrome (SJS). The diagnosis of DRESS is based on a history of MDT ingestion for MB leprosy consisted of dapsone for 6 weeks, and regiSCAR score >5 which indicates a definite case. The diagnosis of SJS is based on clinical features, which are fever, epidermolysis <10% of body surface area, and lesions on the oral mucosa and eyes. The first skin biopsy showed histologic features of exanthematous drug eruption, and the second skin biopsy showed epidermolysis in accordance with SJS. The management of this patients has been adjusted to the guidelines for DRESS and SJS. Management for DRESS are discontinuing the suspected drug, fluid and electrolyte therapy, nutritional therapy, corticosteroids, supportive therapy, and skin care. While the management for SJS are discontinuing the suspected drug, fluid and electrolyte therapy, nutritional therapy, skin care, eye care, oral care, and systemic corticosteroids.

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The incidence of SJS/TEN is 1-2 cases per 100.000 cases per year. Drugs suspected in SJS/TEN are allopurinol, anticonvulsants, lamotigrine, nevirapine, sulfonamides, and NSAIDs. The average onset of SJS/TEN is 5-28 days after ingestion of the causative drug. In general, the SJS/TEN mortality rate is 22% (Creamer et al, 2016).