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Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS) Syndrome Associated with Liver Injury in Patient with Spondylarthritis: A Case Report

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ABSTRACT

Introduction: Drug reaction with eosinophilia and systemic symptoms syndrome or DReSS is a rare and life-threatening severe hypersensitivity reaction characterized by multiorgan involvement, with the liver as the common visceral manifestation. Approximately 10% of patients showed no changes in their eosinophil count. Sulfasalazine and non-steroidal anti-inflammatory drugs are frequently associated with DReSS. The diagnosis of this syndrome remains challenging due to the variety of clinical presentations. **Case Illustration:** We reported a 48-year-old woman who presented with pruritic generalized morbilliform eruption accompanied by facial edema and fever. Five weeks prior, she was treated with sulfasalazine and diclofenac sodium for spondyloarthritis. Her laboratory results showed elevated liver, suggesting drug-induced liver injury. DReSS syndrome was diagnosed by applying the European RegiSCAR. A favorable outcome and recovery of liver function are significantly seen after withdrawal of the suspected drugs, supportive treatment, and administration of systemic corticosteroid. **Discussion:** Sulfasalazine was one of the drugs frequently reported to cause DReSS syndrome. Liver involvement ranges from reversible elevation of liver function tests to hepatic necrosis. Withdrawal of causative drugs and administration of methylprednisolone were recommended, particularly for DReSS with liver involvement. **Conclusions:** DReSS syndrome can manifest with typical skin lesions and multiorgan involvement despite the absence of eosinophilia. The leading cause of mortality related to acute liver injury ranges from mild transaminase to acute liver failure. Prompt cessation of the culprit drug, immunosuppressive therapy, and a multidisciplinary approach might prevent further complications and mortality.

1. INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DReSS) syndrome is a rare and life-threatening severe hypersensitivity reaction characterized by cutaneous eruption, hematological abnormalities, lymphadenopathy, and multiorgan involvement.[1,2] The DReSS usually uses a lowercase e as eosinophilia is absent in 10% of patients.[2,3] The nomenclature DreSS is globally used, although the Japanese consensus group uses the term "Drug-induced hypersensitivity syndrome (DiHS) to diagnose DReSS syndrome with the additional requirement of viral reactivation.[2] The incidence of DReSS syndrome is more than 1 case per 10.000 exposure to medications, with a mortality rate varying from 3,8% to 10%.[2,4] DReSS can occur in all ages, although the mean age of onset is between 40 and 60 years old.[2] Gouive et al. reported DReSS as the most frequent severe cutaneous adverse drug reaction (SCAR) related to hospital admission compared to other SCARs.[5]

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The exact pathogenesis of DReSS remains unclear. However, there were three main interaction components: drug exposure, genetic predisposition related to specific human leukocyte antigen (HLA such as HLA-A*31:01, related to DreSS due to carbamazepine, and viral reactivation, including human herpes virus-6, human herpes virus-7, cytomegalovirus (CMV), Epstein-Barr virus(EBV), and herpes simplex virus (HSV).[1,2,6-7] Each component's cumulative risk factors and predisposing conditions lead to an inflammatory response mediated by T lymphocytes and other cytokines, such as IL-2, IL-6, IFN-γ, TNF-αα, and granulysin, which have been reported to be involved in tissue damage.[1,2,8]

Sulfa drugs are one of the major drugs associated with DReSS, alongside anticonvulsants, allopurinol, NSAIDs, antibiotics, and antihypertension drugs.[2,9–12] In most cases, the symptoms of DReSS are delayed between 2 and 6 weeks after the offending drug is administered.[1,11] Due to the delayed onset and variation in clinical features, diagnosing DReSS can be challenging. The Registry of Severe Cutaneous Adverse Reactions scoring (RegiSCAR) group proposed scoring criteria frequently used to diagnose DreSS. With the early recognition of DReSS syndrome, giving the appropriate treatment, which consists of withdrawal of the suspected drug, supportive care, and systemic corticosteroid, might reduce the disease progression.[13] In this case report, we present the clinical manifestation, how to diagnose, and an appropriate treatment in managing DReSS syndrome.

2. CASE ILLUSTRATION

We present a 48-year-old woman admitted to the Dermatology and Venereology, Faculty of Medicine, University of Indonesia, Jakarta, with a generalized morbilliform eruption accompanied by facial edema and fever (38°C). Five weeks prior, she was given sulfasalazine and diclofenac sodium for spondyloarthritis. The patient has a history of drug allergy due to sulfa antibiotics during childhood. She has a history of metabolic syndrome consisting of hypertension, hypercholesterolemia, and being overweight. Three days prior, she developed a pruritic and painless maculopapular eruption that started from the back and chest and progressed to the trunk, neck, and upper and lower extremities. Physical examination revealed a diffuse maculopapular and target-like lesion on the trunk and extremities, involving more than 50% of the body surface area (BSA) and prominent facial edema. There was no mucosal involvement or enlargement of lymph nodes (Figures 1 and 2).

Her blood work showed elevated liver function, with AST at 504 U/L, ALT at 526 U/L, total and direct bilirubin at 3.35 mg/dL and 2.58 mg/dL, respectively, Gamma GT at 429 U/L, and C-reactive protein at 75.2 mg/L. Meanwhile, other laboratory results, such as hemoglobin at 12.2 g/dL, leukocyte count at 5.03 x 10^9/L, and eosinophil level at 0.4%, were within normal ranges. The viral markers (Hepatitis HAV IgM, HSV1 IgM) were non-reactive. Chest x-ray and echocardiogram showed normal results. From physical examination, there were no signs and symptoms of kidney, pulmonary, cardiovascular, gastrointestinal, endocrine, or neurological involvement. A detailed history taking, clinical, and laboratory examination ruled out other differential diagnoses (autoimmune disease, viral exanthema, other SCAR).

DReSS syndrome was diagnosed by applying the European RegiSCAR, with a total score of 4 (probable case) (Table 1). We also used the Naranjo score for the suspected drug of sulfasalazine with a total score of 5 (probable). The suspected drugs were withdrawn, supportive treatment was provided, and methylprednisolone 31.25 mg (equivalent to prednisone 1.3 mg/kg/day) was administered with gradual tapering to methylprednisolone 15.625 mg (equivalent to prednisone 0.7 mg/kg/day). The patient was discharged with oral methylprednisolone at the following doses: 32 mg daily for 3 days, 24 mg daily for 3 days, 20 mg daily for 3 days, 16 mg daily for 2 weeks, 12 mg for 2 weeks, and 8 mg for 2 weeks. Three months after treatment, a favorable outcome and recovery of liver function were observed, facilitated by collaboration with a hepatologist and rheumatologist. During the six-month follow-up, no similar symptoms or sequelae occurred.

Figure 1.
(1A) Prominent facial edema and maculopapular eruption on the face, (**1B)** Diffuse maculopapular and target-like eruption on trunk and extremities involving more 50% body surface area.

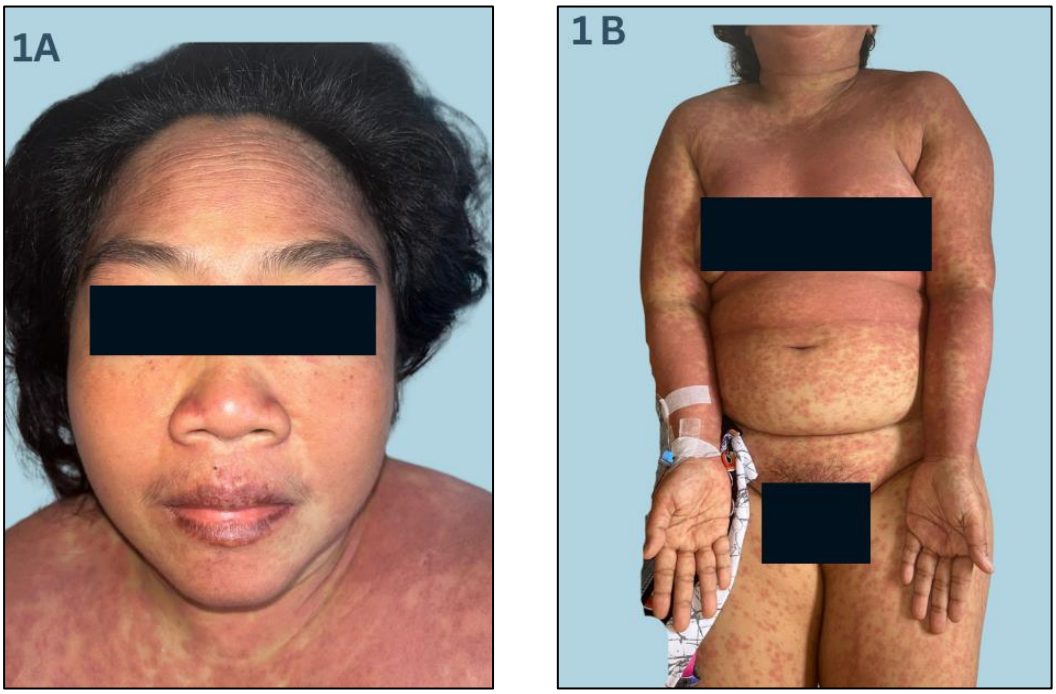

Figure 2.
Hyperpigmented macules with white scale on face, trunk, and extremities involving 2% body surface area 4 weeks after treatment.

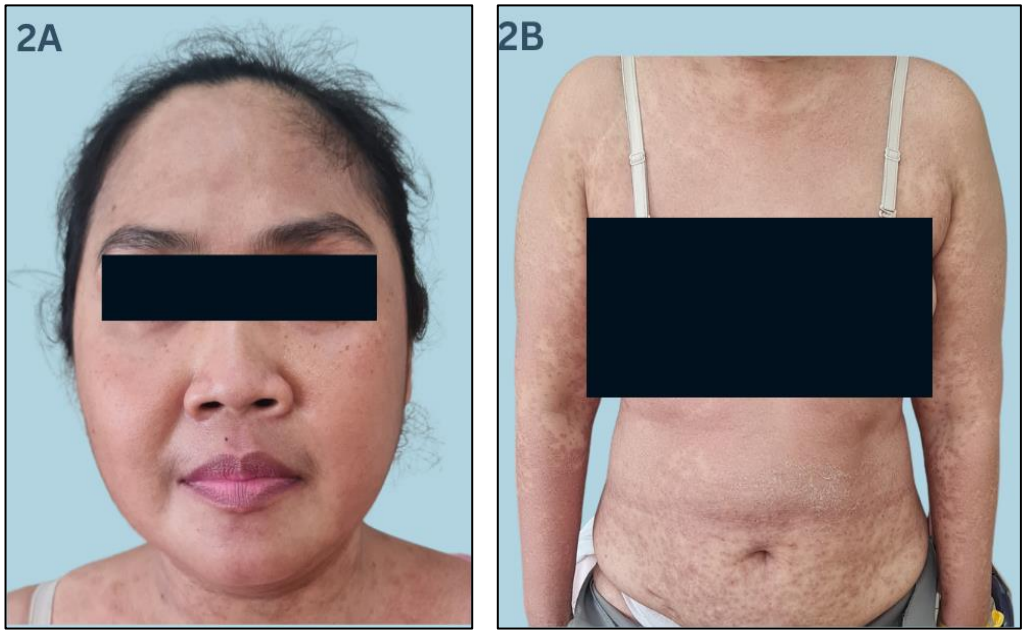

Table 1.
RegiSCAR Criteria[13]

RegiSCAR criteria	No	Yes	Unknown
Fever ≥38.5 °C	-1	0	1
Enlarged lymph nodes (≥2 sites, >1cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0		0
700-1.499 or 10%-19.9%		1	
≥1.500 or ≥20% if leukocyte <4x10^9/L		2	
Skin rash	0		0
Extent >50%	0	1	0
At least 2 of: edema, infiltration, purpura, scaling	-1	1	0
Biopsy suggestive of DReSS	-1	0	0
Internal organ involved*	0		0
1		1	
≥ 2		2	
Resolution in >15 days	-1	0	1
≥3 negative biological investigations to exclude alternative diagnosis Serology HAV, HBV, HCV: non-reactive	0	1	0
Total scoring <2 (no case), 2-3 (possible case), 4-5 (probable case), >5 (definitive case)		+4	

***Internal organ involvement**

Liver (any 1 criterion)
- ALT (526 U/L): > 2X UNL
- D- bil (2,58 mg/dL): > 2x UNL
- AST (504 U/L) , T-bil (3,35 mg/dL), ALP (305 U/L): >2x UNL

Renal (any 1 criterion)
- Creatinine 1,5x patient's baseline
- Twice on successive dates OR proteinuria >1g/day
- Haematuria
- Decrease creatinine clearance, or decreased GFR

Lung (any 1 criterion)
- Evidence of interstitial lung disease (CT, Chest X-ray)
- Abnormal BAL or biopsy specimen or abnormal blood gases

Muscle/ heart (any 1 criterion)
- Elevated serum CPK >2x UNL
- Elevated isoenzyme fractions: CPK-MM (skeletal muscle), CPK-MB (cardiac musle)
- Elevated troponin T (>0,01 µg/L)
- Abnormal imaging including Chest X-ray, echocardiogram, ECG, EMG, CT, or MRI)

Pancreas (any 1 criterion)
- Amylase and/ or lipase >2 X UNL

Other organ: spleen, thyroid gland, central nervous system (CNS), gastrointestinal tract after exclusion of other explanations

ALT: Alanine transaminase, ALP: Alkaline phosphatase, ANA: antinuclear antibody, CPK: creatine phosphokinase, CPK-MB: creatine phosphokinase-muscle/brain, CPK-MM: creatine phosphokinase-muscle type, CT: computed tomography, D-bil: direct bilirubin, DReSS: drug reaction with eosinophilia and systemic symptoms, ECG: electrocardiography, EMG: electromyography, GFR: glomerular filtration rate, MRI: magnetic resonance image, UNL: upper normal limit

3. DISCUSSION

DReSS syndrome is a drug-induced severe cutaneous adverse reaction (SCAR) presenting with skin and multi-organ involvement. [1,2,14] Although eosinophilia is the key element of this

syndrome, it is not always present, as a third of cases showed a normal eosinophil count. In our case, although the eosinophil count is within normal limits, a clinician should consider the entire clinical reasoning process to determine whether the drug groups have the highest risk of DReSS as a suspected drug, and should consider other clinical and laboratory results of the patient.[15] To know the suspected drug, a detailed history of the drug taken, including over-the-counter medications and herbal products taken during the exposure window, must be recorded.[12]

In our case, the suspected drug was sulfasalazine, given 5 weeks before the skin manifestation, which fulfilled the exposure period of 2-6 weeks in DReSS syndrome. Sulfasalazine was frequently reported to cause DRESS syndrome.[1,9] Shear et al. reported that in sulfonamide-related DReSS, there was a high incidence of N-acetyltransferase deficiency, and the preferred CYP450 pathway leads to toxic levels of hydroxylamine metabolites, causing cell damage and immune activation.[12,16]

Our patient presented with maculopapular rash, target-like lesions, facial edema, and fever, which were in line with most of the sulfasalazine-induced DReSS syndrome case reports.[9,10,17] Facial edema is also characteristic of DReSS and might be a differentiating feature from other maculopapular eruptions. However, the exact mechanism of facial edema remains unknown and may be related to the vascular endothelial growth factor pathway.[18]

This patient was having moderate liver injury with elevated values ≥5x for ALT, ≥2x for ALP, and ≥2x total bilirubin from the upper limit level. In sulfasalazine-related DReSS, the main reported liver involvement varies from reversible elevated liver function tests to hepatic necrosis that might progress to liver failure as the leading cause of death in DReSS syndrome.[12,19]

According to Calle et al., this patient was diagnosed with severe DReSS due to moderate to severe liver involvement. This patient fulfilled more than two categories of Drug-Induced Liver Injury (DILI), which are ALT ≥5, ALP ≥2, and total bilirubin ≥2 times the upper limit level.1 Withdrawal of the suspected drug is the main principle for treating DRESS and other cutaneous drug eruptions.[1,20]

Systemic corticosteroids are recommended to control the symptoms and prevent the development of autoimmune reactions. Systemic corticosteroids, such as prednisolone (1 mg/kg/day), should be administered, which is in line with our patient's treatment with methylprednisolone equivalent to 1.3 mg/kg/day prednisone, and with gradual tapering off. The use of methylprednisolone was a systemic corticosteroid that was recommended for DReSS syndrome with liver involvement and the presence of stage 2 or 3 liver injury or DILI.[12]

Chiou et al. observed that patients treated with systemic corticosteroids showed significant improvement in both clinical and laboratory results, with a reduced incidence of secondary skin and soft tissue infections. Signs and symptoms of DRESS might persist even after withdrawal of the causative drug and take approximately 6-9 weeks. [2,20]

In DReSS syndrome, it was proposed to have Treg function loss and autoantigen tolerance; thus, there is an increased risk of developing auto immunities such as thyroiditis, hemolytic anemia, and SLE. Therefore, it is essential to have a long-term follow-up to monitor the development of autoimmune disease and subsequent drug reactions.[1,21,22] The limitation of this case report is that there were some incomplete data, including the skin biopsy result, which could have strengthened the diagnosis of the DReSS syndrome.

4. CONCLUSION

DReSS syndrome can be a potentially life-threatening condition if not identified and managed promptly. A diagnosis of DReSS syndrome should be considered in any patient with suspected drug groups by performing a detailed history taking. It can manifest with an absence of eosinophilia, typical skin lesions, and multiorgan involvement. Hepatic necrosis is the leading cause of mortality in DReSS. In our case, early recognition with cessation of suspected drug(s), immunosuppressive therapy using systemic corticosteroid, and a multidisciplinary approach can prevent complications and mortality. Long-term follow-up should also be considered to monitor the syndrome's sequelae.

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6. CONFLICT OF INTEREST

The author declares no conflict of interest.

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