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Case Report

Drug reaction with eosinophilia and systemic symptoms resulting from allopurinol

Nanda Earlia[1], Fitri Dewi Ismida[2], Aqil Yuniawan Tasrif[3], Mahda Rizki Liana[3], Mikyal Bulqiah[3], Teuku Hidayat Syah[3], Muhammad Taqy Adzkia Zaldi[3], Muzaki[3]

[1] Dermatovenereology Department Faculty of Medicine Universitas Syiah Kuala/Dr. Zainoel Abidin Regional General Hospital, Banda Aceh, Aceh, Indonesia.
[2] Pathology Anatomy Department Faculty of Medicine Universitas Syiah Kuala/Dr. Zainoel Abidin Regional General Hospital, Banda Aceh, Aceh, Indonesia.
[3] Faculty of Medicine Universitas Syiah Kuala/Dr. Zainoel Abidin Regional General Hospital, Banda Aceh, Aceh, Indonesia.

Abstract Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe drug reaction to the skin that is characterized by fever, lymphadenopathy, hematological abnormalities, involvement of internal organs, and reactivation of the virus. Allopurinol and other drugs are only a few of the medications that have been linked to DRESS. A Male, 42 years old, referred from a regional hospital, with complaints of reddish rash all over the body since 5 days. Physical examination revealed elevated body temperature. dermatologic status appeared to be obvious macules and erythematous patches with fuzzy boundaries, a variety of shapes, a large number, guttate to plaque size, confluent arrangement, and universal distribution in the facial, thorax, upper and lower extremities regions. This complaint arose after the patient took a high dose of allopurinol. Blood laboratory examination revealed eosinophilia, leukocytosis, elevated liver enzymes, and hypoalbuminemia. After treatment with steroid injections and topical creams and discontinuation of previous medications, there was clinical improvement. DRESS is a severe multiorgan hypersensitivity reaction that is mostly caused by a limited number of drugs in patients with a genetic predisposition. Accumulation of oxypurinol, especially in patients with decreased renal clearance, increases the risk of developing DRESS syndrome.

Key words
Drug reaction; Eosinophilia; Systemic symptoms; Allopurinol; Elevated liver enzyme.

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe drug reaction to the skin that is characterized by fever, lymphadenopathy, hematological abnormalities, involvement of internal organs, and reactivation of the virus.[1] Genetics, viruses, and environmental factors combine intricately to develop DRESS. Although the precise pathophysiology of DRESS is still not fully understood, it is generally accepted that it is a T-cell-mediated hypersensitivity reaction to medications. Allopurinol, anticonvulsants (carbamazepine, lamotrigine, phenytoin, phenobarbital, valproic acid), antimicrobials (sulfasalazine, dapsone, trimethoprim-sulfamethoxazole, vancomycin), and antivirals (nevirapine, abacavir, zalcitabine) are only a few of the medications that have been linked to DRESS.[2,3] With numerous research demonstrating specific human leucocyte antigen (HLA) alleles to be a significant risk factor with

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Address for correspondence
Dr. Nanda Earlia, Dermatovenereology Department, Faculty of Medicine, Universitas Syiah Kuala/Dr. Zainoel Abidin Regional General Hospital, Banda Aceh, Jl. Teuku Moh. Daud Beureueh No. 108, Bandar Baru, Kuta Alam, Banda Aceh 24415, Aceh, Indonesia.
Ph: +628126900979
Email: nanda.earlia@unsyiah.ac.id

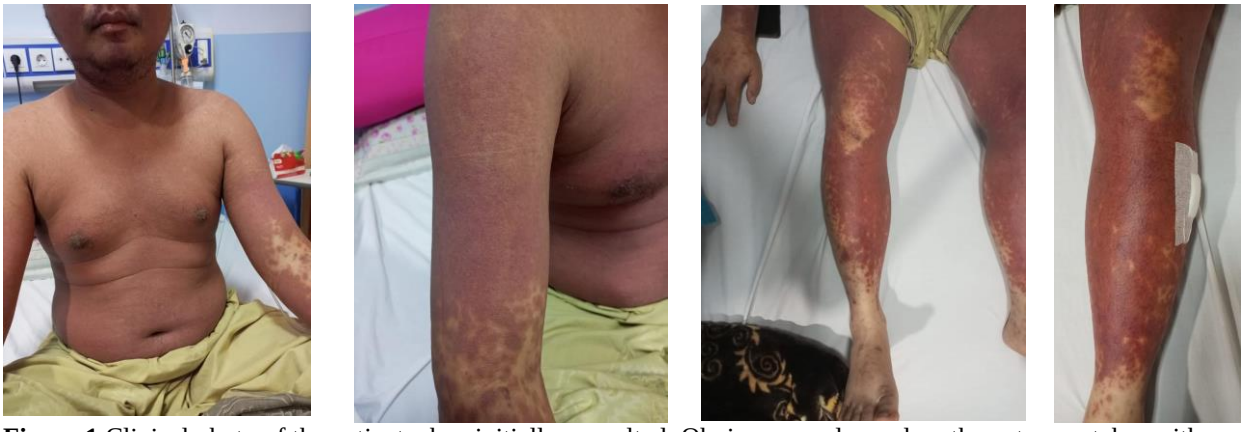

Figure 1 Clinical photo of the patient when initially consulted. Obvious macules and erythematous patches with fuzzy boundaries, a variety of shapes, a large number, guttate to plaque size, confluent arrangement, and universal distribution in the facial, thorax, upper and lower extremities regions.

exposure to specific medications, other studies have demonstrated a substantial relationship between ethnic background and DRESS.[4] Epilepsy, human immunodeficiency virus (HIV), hypertension, diabetes, and hyperuricemia are the most prevalent DRESS comorbidities. These co-occurring diseases are probably linked to the substance that caused them rather than an innate propensity to DRESS.[4] The quick cessation of the potentially implicated medicine and vigorous supportive care is the most crucial management actions.[5]

Case Report

A 42-year-old male was referred patient from the regional hospital, consultation from the Internal Medicine to the Department of Dermatology and Venereology with complaints of a red rash all over the body for 5 days before hospital admission. As the patient's temperature rises, the rash first appears behind the patient's ears and neck before moving onto the face, chest, hands, and feet. A fluctuating fever is present. The patient has a diminished appetite and seems lethargic. The patient suffers from bronchial asthma and gouty arthritis. Daily, the patient took allopurinol 300 mg tablets twice a day, colchicine 0.5 mg tablets twice a day, and methylprednisolone 8 mg tablets three times a day. Physical examination revealed obvious macules and erythematous patches with fuzzy boundaries, a variety of shapes, a large number, guttate to plaque size, confluent arrangement, and universal distribution in the facial, thorax, upper and lower extremities regions.

The results of blood laboratory tests during treatment are presented in the **Table 1**.

Table 1 Results of patient laboratory tests during treatment

Lab Examination	*First Results*	*Second Results*	*Normal Value*
Hemoglobin	**18.3**	14.8	14.0-17.0
Hematocrit	52	**42**	45-55
Erythrocytes	**6.2**	5.0	4.7-6.1
Platelets	235	245	150-450
Leukocytes	**34.74**	33.92	4.5-10.5
Eosinophils	**11**	**8**	0-6
Basophils	0	1	0-2
Rod Neutrophils	**0**	0	2-6
Segment neutrophils	63	62	50-70
Lymphocytes	**15**	**19**	20-40
Monocytes	**11**	**10**	2-8
Aspartate aminotransferase (AST)	**884**	**267**	<35
Alanine transaminase (ALT)	**1156**	**781**	<45
Albumin	**2.80**	**2.85**	3.5-5.2
Calcium	7.6	-	8.6-10.3
Urea	**46**	38	13-43
Creatinine	**2.20**	1.01	0.67-1.17
Natrium	**130**	-	132-146
Kalium	4.6	-	3.7-5.4
Chloride	104	-	98-106

Description: Numbers in bold are interpreted as not within normal limits.

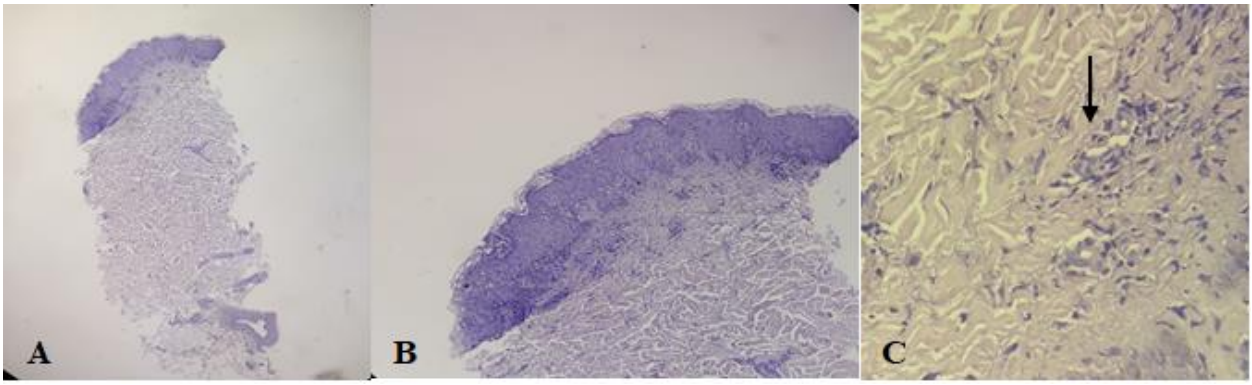

Figure 2 Histopathological examination results. (A) Observation of the specimen with 40X magnification and staining with hematoxylin-eosin; (B) Observation of the specimen with 200X magnification and hematoxylin-eosin staining found chronic inflammation; and (C) Observation of the specimen with 400X magnification and hematoxylin-eosin staining found a layer of lymphocyte cells (black arrow).

The patient was diagnosed with DRESS. Advice from the Department of Dermatology and Venereology for treatment given an injection of methylprednisolone 62.5 mg per 8 hours, desoximetasone cream 0.25% + 60-gram vaseline album smeared in the morning and afternoon, and clobetasol propionate 0.1% cream + 60-gram vaseline album smeared at night. Histopathological examination showed that the epidermis layer consisted of keratinized stratified squamous cells with mild acanthosis with cell nucleus morphology within normal limits. In the subepidermal layer, it consists of fibro collagenous connective tissue that is localized lightly with lymphocyte cells, which can be concluded as chronic non-specific inflammation.

On the fifth day of follow-up, the lesions improved, therapy was continued, and the Department of Internal Medicine planned to discharge the patient from the hospital. The patient is planned to be tested for provocation and skin patch test in the next 6 months.

DRESS is a severe multiorgan hypersensitivity reaction that is mostly caused by a limited number of drugs in patients with a genetic predisposition.[1] On investigation, it was found that there were abnormalities in the laboratory examination in the form of eosinophilia above normal values and lymphocytes below normal limits. In addition, there is evidence of involvement of internal organs, namely the liver, which is characterized by an increase in AST 884 g/dL and ALT 1156 g/dL and an increase in kidney function based on levels of urea (46 g/dL) and creatinine (2.20 g/dL). Liver involvement can progress to liver failure, this is thought to be the main cause of death in DRESS.[5] In addition to the liver, an increase in the results of kidney function tests was also reported to be frequently increased in patients with DRESS syndrome.[6] As many as 50% of cases with DRESS that experience kidney failure are allopurinol-induced DRESS.[3]

In previous studies, it was stated that Allopurinol is a type of drug that often causes allergic drug eruptions. Allopurinol, a purine inhibitor of the enzyme xanthine oxidase (XO), inhibits the uric acid synthesis and has become a commonly used drug for hyperuricemia. By inhibiting XO, allopurinol, and its major metabolite alloxanthin (oxypurinol) prevent the conversion of hypoxanthine to xanthine and uric acid. It provides resolution of symptoms in most cases with gout; 53% of patients receiving allopurinol 300 mg daily achieved optimal plasma urate concentrations. However, in some patients, these drugs are not well tolerated and occasionally cause severe hypersensitivity

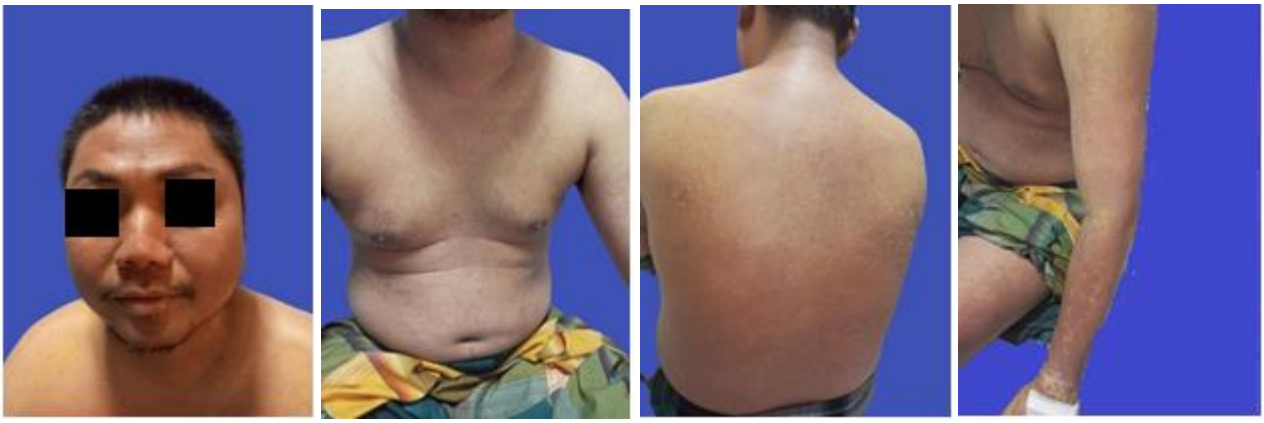

Figure 3 Clinical photo of the patient (improvement). Lesions in the facial, thorax, upper and lower extremities regions, showed macules, and erythematous patches have diffuse borders, different forms, guttate to plaque size, multiple numbers, confluent arrangement, and generalized distribution.

reactions.[7] The pathophysiology of the allopurinol-induced DRESS syndrome appears to be related to the accumulation of oxypurinol in patients with renal insufficiency.[7] Accumulation of oxypurinol, especially in patients with decreased renal clearance, increases the risk of developing DRESS syndrome.[8]

The European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (Regi SCAR) group recommends diagnostic criteria for hospitalized patients with a drug rash with suspected DRESS. The diagnosis of DRESS can be made if it meets 3 of the criteria below **(Table 2)**.[3,5]

Based on the history, physical examination, and investigations, the patient met 5 of the 7 criteria (acute skin rash, fever, involvement of at least 1 internal organ, lymphocytes below normal values, and eosinophilia) based on the diagnostic criteria according to Regi SCAR. Administering corticosteroids to DRESS aims to treat symptoms and prevent further damage. Fitzpatrick *et al*. recommend giving prednisone at a dose of 0.5-1 mg/kg body weight. This dose is maintained until there is no further exacerbation of the disease. After that, the dose can be reduced slowly with an average decrease of 20% per day.[6] The patient, in this case, received systemic corticosteroid treatment, namely intravenous methylprednisolone 62.5 mg/ 8 hours which is equivalent to a dose of prednisone 1 mg/ kg body weight. The prognosis of DRESS depends on the causative drug, viral reactivation involved, and systemic organ involvement. DRESS induced by allopurinol and minocycline is more severe with a prolonged course of the disease. The DRESS mortality rate is estimated at 10%.[10]

Table 2 The DRESS diagnostic criteria according to Regi SCAR.

No.	*Criteria*
1.	Acute skin rash
2.	Fever (>38^{o}C)
3.	Enlargement of lymph nodes >2 locations
4.	Involvement of at least 1 internal organ
5.	Lymphocytes are below or above normal
6.	Eosinophilia
7.	Thrombocytopenia

Abbreviations

ALT: Alanine transaminase

AST: Aspartate aminotransferase

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

HIV: Human Immunodeficiency Virus

HLA: Human Leucocyte Antigen

Regi SCAR: The European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples

XO: Xanthine oxidase

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Author's contribution

NE: Identification, diagnosis & Management of the case, critical review, has given final approval of the version to be published.

FDI: Diagnosis and management of the case, critical review, has given final approval of the version to be published.

AYT,MRL,MB,THS,MTAZ,M: Identification of the case, manuscript writing, has given final approval of the version to be published.

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