

## Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome: A Case Report and Literature Review

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### Abstract

**Background:** DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) is an uncommon severe systemic hypersensitivity drug reaction. All antituberculous drugs have a risk to induce drug hypersensitivity syndrome of which Rifampicin is the most prevalent.

**Case presentation:** In this report, we describe a clinical case of 62-year-old man who experienced the typical clinical course of DRESS syndrome caused by Rifampicin. Clinical manifestation (fever, facial edema, widespread skin lesions, internal organ involvement, and haematological abnormalities) occurred within 4 weeks after empirical treatment of prosthetic valve endocarditis. Symptoms improved after discontinuation of antibiotics and a culprit drug was confirmed by allergological skin patch testing.

**Conclusion:** Due to possibility of various systemic manifestations, diagnosis of DRESS syndrome is often overlooked but it should be considered for its severe complications.

rate is about 10% [3,4]. Most common early symptoms of the DRESS syndrome are polymorphous skin rash and fever. Typically, these signs are associated with multiple internal organ involvement, lymphadenopathy and haematological abnormalities [1,3,5,6]. The prevalence of DRESS according to age is most common in patients older than 50 years [6,7] and the incidence of the overall population is between 1 in 1000 and 1 in 10,000 drug exposures [4,7,8]. Antiepileptic agents, Allopurinol and sulphonamides are the most frequently reported culprit drugs [2,7,8]. Although DRESS syndrome caused by antituberculous drugs is less common, the evaluation is necessary considering its serious clinical manifestation and the importance of discontinuation of the suspected drug [8,9]. According to the literature, all antituberculous drugs have a risk to induce drug hypersensitivity syndrome of which Rifampicin is the most prevalent culprit drug for its larger list of indications [8,10,11]. However, due to its variable, delayed manifestation and low incidence DRESS syndrome is often overlooked [4]. Moreover, from 10 to 20% of cases fulfilling the diagnostic criteria for DRESS, a relationship with a drug still cannot be established [12].

In this report we describe a clinical case of 62-year-old man who experienced typical symptoms and course of Rifampicin induced drug hypersensitivity syndrome and was confirmed by allergological skin patch testing.

**Keywords:** Drug reaction; Antituberculous drugs; Rifampicin; Drug hypersensitivity

### Introduction

Drug hypersensitivity syndrome reported under various names, commonly called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe adverse drug reaction that usually develops within 2-8 weeks of initiation of drug therapy [1,2]. It is a life-threatening condition and its mortality

### Case Report

On 24 August 2018, a 62-year-old man was hospitalized in the Department of Internal Medicine of the Republican Siauliai County Hospital for fever of unknown origin. The patient complained of general weakness, fever up to 39°C. Symptoms started 1 week ago, consequently, the patient was consulted by the physician and the antibacterial treatment with Cefuroxime was prescribed, yet no effect was observed.

It was known that the patient underwent a mitral valve prosthetic surgery with a mechanical prosthesis and a tricuspid valve annuloplasty on 13 July 2018 due to significant leakage of a mitral and tricuspid valve. Also, the patient was previously diagnosed with primary arterial hypertension, gout for around 30 years, chronic atrial fibrillation, secondary anaemia, and trophic ulcers, which were corrected with skin plastics.

Blood and urine microbiological cultures were obtained in the Department of Internal Medicine. Suspecting the prosthetic valve endocarditis, a transesophageal echocardiographic study was performed during which a formation on the mitral valve prosthesis was observed. For further treatment of prosthetic valve endocarditis, the patient was transferred to the Department of Cardiology on 31 July 2018.

Physical examination showed pale mucosa, normal arterial blood pressure with arrhythmia due to chronic atrial fibrillation. Lung auscultation and palpation of the abdomen were also normal. There were scars on the right leg observed after the previous skin plastics.

Since blood and urine microbiological cultures were negative, according to the Guidelines for treating infectious endocarditis (2016) by the European Society of Cardiology, antibacterial treatment with Vancomycin, Gentamicin, and Rifampicin were started. The treatment was tolerated well by

the patient. Bloodwork (**Table 1**) and transesophageal echocardiogram were repeated and reduced inflammatory parameters with decreasing vegetation on the mitral valve prosthesis were observed. The chest X-ray showed no infiltration or specific local changes. During the abdominal and renal ultrasound examination, chronic damage of liver (steatofibrosis, hepatomegaly), pancreas (lipidosis), renal (right kidney nephropathy, cysts) was reported as well as minimal splenomegaly.

Two weeks after the beginning of the treatment, dizziness when standing up, nystagmus on the left side emerged. The patient was consulted by a neurologist, computed tomography of the brain was performed, but acute pathology was not found. Gentamicin was discontinued due to ototoxicity, leaving double antibacterial therapy.

One month after the beginning of the treatment, the patient began to feel tingling in the whole body after vancomycin infusion; therefore Clemastine was prescribed before the infusion. After a few days, a pink maculopapular rash appeared on the patient's chest, which spread to the face and the whole body, then merged (**Figure 1**). Facial edema was also observed. The fever went up to 40°C, leukocytosis with eosinophilia appeared, CRP levels increased, renal and hepatic insufficiency was followed (**Table 1**).



**Figure 1:** Skin rash on 5 October 2018.

The patient was discussed in the Consilium with cardiologist, allergologist and clinical immunologist, microbiologist: suspecting possible drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, it was decided to discontinue antibacterial therapy (duration of antibacterial therapy overall was five weeks), the treatment was started with systemic and local glucocorticoids, antihistamines. Three days later, the patient's condition started to improve, rash throughout the body decreased (**Figure 2**). Clinical and laboratory examinations were improved in dynamics,

vegetation on the prosthesis was not observed, and therefore the patient was discharged home under the family physician's monitoring since 19 October 2018.

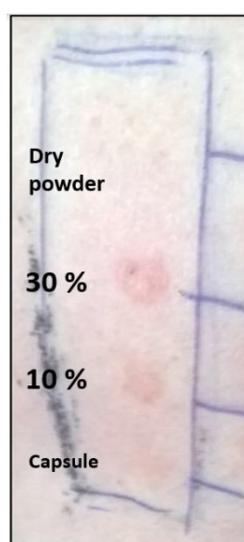
After six weeks the patient was consulted and investigated by the allergologist and clinical immunologist. Patch testing with Rifampicin (100% with dry powder; 30, 10% dilution and capsule) and Vancomycin (30 and 10% in dilution) was performed. Readings on day 2 and 3 showed a positive reaction to Rifampicin (**Figure 3**).



**Figure 2:** Skin rash on 18 October 2018.

**Table 1:** Laboratory tests in dynamics.

Test/Date	Leukocytes × 10 <sup>9</sup> /l	CRP (mg/l)	Eosinophils ×10 <sup>9</sup> /l	AST (U/l)	ALT (U/l)	GGT (U/l)	ALP (U/l)	Creatinine (μmol/l)	Urea (mmol/l)	Potassium (mmol/l)
Laboratory reference ranges	3.6-11.0	<5	0.1-0.4	<50	<50	<55	30.0-120.0	72.0-127.0	2.8-7.2	3.5-5.1
31/08/2018	11.8	25.1	0.1	48.8	35.9	83.0	98.0	96.0	6.3	4.76
10/9/2018	5.2	8.5	0.3	-	-	-	-	150.0	6.4	4.90
3/10/2018	12.3	29.3	1.1	52.7	49.5	175.0	185.0	168.0	6.2	4.68
18/10/2018	9.5	3.3	0.1	69.4	40.4	205.0	123.0	109.0	6.2	4.3



**Figure 3:** Positive patch test with Rifampicin.

## Discussion

Clinical manifestation of DRESS syndrome is characterized by fever, widespread skin lesions, internal organ involvement, haematological abnormalities and lymphadenopathy which appears approximately from 2 to 8 weeks after drug intake [1]. The most prevalent but not specific sign is skin lesions [2] and it occurs in 73-100% of the patients [1]. Typically, skin lesions affect more than a half of the body surface area mainly with a maculopapular rash, however, it can occur as pustular, bullous, plaque, patch, target lesion and other forms of skin eruptions [2,3]. Another meaningful sign of the syndrome is facial edema which usually is symmetric, persistent, and associated with erythema and develops up to 76% of cases [4-6]. In our case, most of the body surface was covered by maculopapular lesions with facial swelling.

Symptoms including fever (38 to 40°C), malaise and lymphadenopathy are also not specific. Diffuse lymphadenopathy is reported in 30 to 60% of cases [7]. Hematological abnormalities is another group of signs with eosinophilia and atypical lymphocytes as most common changes while lymphocytosis, leukocytosis, neutrophilia, monocytosis occur less frequently [6,8,9]. Involvement of at least one visceral organ occurs approximately 90% of patients

[2,9]. Most commonly involved organs are liver and kidney. Hepatitis, hepatosplenomegaly with elevated serum alanine aminotransferase (ALT) are found in approximately 70% of patients with DRESS and liver damage is the main cause of mortality [10]. However, the severity of a liver injury is not related to the causative drugs [5]. Renal abnormalities are the second most involved organ system and are associated with the older age and underlying renal or cardiovascular diseases [5,11]. Kidney injury should be defined as creatinine level 50 % above baseline [12]. Pulmonary involvement may also be present and other organs such as gastrointestinal tract, spleen heart, pancreas, thyroid, brain, muscle, eyes could be damaged [7,8]. The skin eruption and visceral involvement generally decrease gradually after drug removal. The average time of recovery is 6-9 weeks. Only 20% of cases symptoms persist longer than a few months [5].

The pathomechanism of DRESS syndrome is not yet fully understood. Current evidence shows interaction between a genetic deficiency of detoxifying enzymes, genetic associations between HLA antigen and possible virus-drug interaction [5,10,13-15]. Reduction of some enzyme activities leads to accumulation of drugs which may elicit immune responses [5]. Some of human herpes viruses, especially HHV-6, have a role in the pathomechanism of the syndrome. The antibody titer of HHV-6 increases in approximately 43-100% of patients 2-4 weeks after the onset of symptoms [16,17]. It proves that the role of HHV-6 is significant and unique in DRESS syndrome.

Reactivation of other viruses, such as HHV-7, EBV, CMV was also detected [5,18,19].

The diagnosis of DRESS is suspected in a patient who received new drug treatment from 2 to 8 weeks and presents previous symptoms, especially visceral involvement. Diagnosis is based on criteria included in the scoring system proposed by the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group (**Table 2**) [4,8]. The diagnosis of DRESS syndrome is then made on the total score: <2 points: no case; 2-3 points: a possible case; 4-5 points: a probable case; >5 points: definite case. However, score system includes some information that is available only in a later time (e.g. >15 days) of disease due to this it may serve as a guidance for a diagnostic process [2]. In addition to this test for virus infection could be done. Furthermore, allergological work up for the culprit drug recognition should be performed after the remission of DRESS. In our case, the score was estimated of 6-0 for fever, 0 for enlarged lymph nodes, 1 for eosinophilia, 1 for atypical lymphocytosis, 2 for skin rash, 0 for unknown results of skin biopsy, 2 for liver and renal involvement, 0 because skin resolution was more than 15 days, 0 for undone laboratory tests aimed to exclude other causes (**Table 2**).

Differential diagnosis with other severe drug eruptions, infections, hypereosinophilic syndrome, lymphoma, and autoimmune connective tissue disease are needed. These conditions may mimic DRESS syndrome [20].

**Table 2:** The RegiSCAR scoring system for diagnosing DRESS syndrome [1].

Items	Score			Comments
	-1	0	1	
Fever=38.5°C	N/U	Y		
Enlarged lymph nodes		N/U	Y	>1 cm and=2 different areas
Eosinophilia=0.7 × 10 <sup>9</sup> /L or=10% if WBC <4.0 × 10 <sup>9</sup> /L		N/U	Y	Score 2, when=1.5 × 10 <sup>9</sup> /L or=20% if WBC <4.0 × 10 <sup>9</sup> /L
Atypical lymphocytosis		N/U	Y	
Skin rash				Rash suggesting DRESS:=2 symptoms:
Extent >50% of BSA Rash suggesting DRESS	N	N/U U	Y Y	purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Skin biopsy suggesting DRESS	N	Y/U		
Organ involvement		N	Y	Score 1 for each organ involvement, maximal score: 2
Rash resolution=15 days	N/U	Y		
Excluding other causes		N/U	Y	Score 1 if 3 tests of the following tests were performed and all were negative: HAV, HBV, HCV, Mycoplasma, Chlamydia, ANA, blood culture

N: No; Y: Yes; U: Unknown; ANA: Anti-Nuclear Antibody; BSA: Body Surface Area; HAV: Hepatitis A Virus; HBV: Hepatitis C Virus; HCV: Hepatitis C Virus; WBC: White Blood Cells

Identification and withdrawal of the culprit drug is the mainstay. Empirical treatment with antibiotics or anti-

inflammatory drugs should not be administered for patients with DRESS since they can cause dangerous cross-reactivity between drugs [21,22].

In our case, fever and rash reduced within a few days after withdrawal of Rifampicin and treatment with systemic corticosteroids. However, in a severe liver involvement systemic corticosteroid have no proven benefits. Other management options as cyclosporine, intravenous immunoglobulins or antiviral treatment are discussed as the evidence is limited and more studies are needed [4,22-24].

## Conclusions

In this clinical case, a 62-year-old patient was diagnosed with DRESS syndrome caused by Rifampicin. Clinical manifestation occurred within 4 weeks after the beginning of treatment. The first symptom was skin lesions with facial edema. The eruption started on a chest, leading to other areas covering more than 50% of the whole body. Systemic symptoms and organ involvement were expressed as a typical course of DRESS. Treatment was based on discontinuation of the given drugs and systemic corticosteroids what eventually caused an absence of previous symptoms. Monitoring was recommended with the family physician.

In general, concerning various systemic manifestations, diagnosis of DRESS syndrome should be considered due to a high risk of severe complications. That makes the history of taken medications so important. Symptoms occurrence is prolonged and manifestations as liver insufficiency might be life-threatening. The mortality rate is up to 10%. Due to this withdrawal of causative medications is an essential part in the management of this syndrome.

## Competing Interests

The authors declare that they have no competing interests.

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