



Relapse of Sulfasalazine-Induced DRESS Syndrome Following the Administration of Contrast Media: A Case Report

Niayesh Mohebbi¹, Hamidreza Taghvaye Masoumi², Malihe Khosravi Khezri³, Mona Talaschian^{4*}

1. Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
2. Department of Clinical Pharmacy, Faculty of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran.
3. Department of Clinical Pharmacy, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran.
4. Department of Internal Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Use your device to scan and read the article online



Citation Mohebbi N, Taghvaye Masoumi H, Khosravi Khezri M, Talaschian M. Relapse of Sulfasalazine-Induced DRESS Syndrome Following the Administration of Contrast Media: A Case Report. *Case Reports in Clinical Practice*. 2021; 6(3):94-98.

Running Title: Relapse of DRESS Syndrome with Contrast Media

Article info:

Received: 01 Jun 2021

Revised: 17 Jun 2021

Accepted: 19 Jun 2021

Keywords:

Contrast media; Drug reaction with eosinophilia and systemic symptoms; Hypersensitivity reactions; Sulfasalazine

ABSTRACT

Sulfasalazine, a non-antibiotic sulfonamide, is associated with severe hypersensitivity reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. We report a case of sulfasalazine-induced DRESS syndrome that relapsed following the administration of visipaque® (iodixanol). Macular rashes, pruritus, and an acute exacerbation of dyspnea were immediately observed after the administration of contrast media. It seems that patients suffering from DRESS syndrome are sensitive to the administration of other new medications with a high possibility of hypersensitive reactions. It can be concluded that iodinated contrast media should be used cautiously in patients with DRESS syndrome.

Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare adverse reaction. Only one in 1,000 to

one in 10,000 suffer from DRESS due to drug exposure [1]. Conventional anti-epileptic drugs (carbamazepine, phenytoin, and lamotrigine), allopurinol, vancomycin, sulfasalazine, and sulfamethoxazole are the most common drugs associated with the development of this

* Corresponding Author:

Mona Talaschian, MD.

Address: Department of Internal Medicine, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

E-mail: talaschianmona@gmail.com



drug hypersensitivity reaction [2]. DRESS syndrome is a delayed onset reaction that is usually associated with fever, lymphadenopathy, eosinophilia, rashes on more than 50% of the Body Surface Area (BSA), internal organ involvement, and facial edema [3].

Owing to the high mortality rate, especially in patients with severe drug reactions, rapid diagnosis and treatment are critical [2]. Suspicious offending medication withdrawal is the main treatment for the DRESS syndrome; it may be performed along with pharmacologic intervention, such as systemic glucocorticoids, short-term administration of oral cyclosporine, or intravenous immunoglobulins [4, 5]. Here, we report a case of sulfasalazine-induced DRESS syndrome that exacerbated following the administration of contrast media.

Case Presentation

A 33-year-old woman (60 kg) who had recently been diagnosed with Rheumatoid Arthritis (RA) was admitted to the emergency department of Shariati Hospital, Tehran, with manifestations of facial edema, dyspnea, generalized macular rashes, and pruritus affecting the face, abdomen, and upper and lower limbs (the involved area was more than 50% of BSA) (Figure 1). The patient had been treated with sulfasalazine (500 mg twice daily) and prednisolone (5 mg twice daily) for the past two weeks. We found a fever (38.8°C) accompanied by lymphadenopathy of cervical and axillary lymph nodes during physical examination. We did not observe any mucosal lesions in the assessment of the oral cavity, ocular, and vaginal regions.

Laboratory tests revealed a serum Alanine aminotransferase (ALT) of 494 U/L, Aspartate aminotransferase (AST) of 238 U/L, alkaline phosphatase of 617 U/L, total bilirubin of 1.8 mg/dL, direct bilirubin of 1 mg/dL, serum albumin of 3.02 g/dL, Lactate Dehydrogenase (LDH) of 1447 U/L, International Normalized Ratio (INR) of 1.48, and C-Reactive Protein (CRP) of 167 mg/L.

The blood cell counts were as follows on admission: The White Blood Cell (WBC) count was 46300/ μ L with a 5% eosinophil count (2315/ μ L), while the platelet count was 258000/ μ L, and Hemoglobin (Hgb) was 13.1 g/dL. Other laboratory tests, including serum electrolytes (sodium, potassium, magnesium, calcium, and phosphorus), renal function tests (serum creatinine and blood urea nitrogen), and rheumatologic tests (anti-dsDNA, ANA, C3, C4, CH50, P-ANCA, C-ANCA, anti-Ro/SSA antibodies, and anti-La/SSB antibodies), were all within the reference range. Viral markers (human immunodeficiency virus,

Hepatitis C antibody, and Hepatitis B surface antigen) and cultures (blood, urine, and stool) were all negative.

Pleural effusion was detected in a chest Computerized Tomography (CT) scan. Hand skin biopsy was performed and according to the microscopic report, "the sections showed skin tissue with orthokeratosis, spongiosis, basal cell damage, superficial perivascular lymphocytic infiltration, and lymphocytic exocytosis, and no eosinophils were seen".

In accordance with the presumptive diagnosis of drug-induced hypersensitivity reaction, sulfasalazine was discontinued immediately, and intravenous dexamethasone (4 mg twice daily) was started along with oral hydroxyzine (10 mg three times per day). Fever, lymphadenopathy, and pruritus ameliorated three days after the initiation of glucocorticoid.

On the 20th day of treatment, the cutaneous manifestations of drug reaction and the abnormalities found in the liver function tests partially improved, with the eosinophil count reaching 1%. Therefore, intravenous dexamethasone was replaced with oral prednisolone (10 mg twice daily). One day after this change, the cutaneous manifestations of drug hypersensitivity reappeared. Hence, the glucocorticoid switched back to the previous intravenous dexamethasone (4 mg twice daily) and the relapse was resolved. Five days later, the patient underwent CT angiography with contrast media (IV visipaque® 320 mg) due to persistent dyspnea to exclude Pulmonary Thromboembolism (PTE). Immediately following the procedure, the macular rashes, pruritus, and dyspnea exacerbated; therefore, the dexamethasone dose was increased to 4 mg three times a day. Because the pruritus was annoying for the patient, the hydroxyzine dose was fixed at 25 mg three times per day. Five days later (on day 30th of treat-

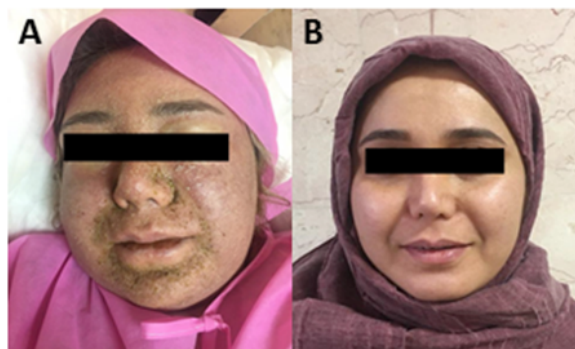


Figure 1. Facial edema, erythema, and macular rashes

A: Before; B: After drug reaction with Eosinophilia, and Systemic Symptoms (DRESS) treatment.

Table 1. RegiSCAR-group diagnosis score for DRESS

Characteristics		No	Yes	Unknown
	Fever $\geq 38.5^{\circ}\text{C}$	-1	0	-1
	Enlarged lymph nodes (≥ 2 sites, >1 cm)	0	1	0
Eosinophilia	700-1499 or 10-19.9%	0	1	0
	≥ 1500 or $\geq 20\%$	0	2	0
	Atypical lymphocytes	0	1	0
	Extent $>50\%$	0	1	0
Skin rash	At least 2 of: Edema, infiltration, purpura, scaling	-1	1	0
	Biopsy suggesting DRESS	-1	0	0
Internal organ involvement	One	0	1	0
	Two or more	0	2	0
	Resolution >15 days	-1	0	-1
	Investigation for alternative cause (blood cultures, ANA, serology for Hepatitis viruses, mycoplasma, Chlamydia) ≥ 3 done and negative	0	1	0
Total score			8	

Final score <2 , no case; final score 2-3, possible case; final score 4-5, probable case; final score >5 , definite case.



ANA: Anti-Nuclear Antibody; DRESS: Drug Reactions with Eosinophilia and Systemic Symptoms.

ment), owing to complete remission of skin rashes, pruritus, lymphadenopathy, liver function test abnormalities, hematological abnormalities, and dyspnea, the patient was discharged with a prescription of oral prednisolone (75 mg daily), with the tapering plan of 5 mg per week.

Discussion

Sulfasalazine belongs to the non-antibiotic sulfonamide family; it is used as an anti-inflammatory agent for the treatment of many rheumatoid diseases, such as RA [6, 7]. It has been demonstrated that sulfonamides are among the most common drugs associated with severe hypersensitivity reactions, including the Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis, and DRESS syndrome [7]. In our patient, the drug reaction occurred two weeks after the initiation of sulfasalazine; this was in accordance with the development of DRESS syndrome. Furthermore, fever (more than 38.5°C), two sites of enlarged lymph nodes, eosinophilia, rashes involving more than 50% BSA, facial edema, the involvement of two internal organs, negative results for other possible causes (blood cultures, ANA, and viral hepatitis), and the disease duration of more than 15 days without the involvement of mucous

membranes caused a high degree of suspicion to DRESS syndrome. According to the result of the skin biopsy, possible diagnoses of drug reaction (not specifically DRESS) and spongiotic and lichenoid tissue pattern were considered. For the diagnosis of DRESS syndrome, we used the RegiSCAR scoring system as valuable diagnostic criteria. The possibility of diagnosis was definite (final score=8) based on the scoring system as shown in Table 1 [8, 9]. Although no randomized clinical trial has been done regarding the treatment of DRESS syndrome, systemic glucocorticoids (0.5–1.0 mg/kg/day prednisolone or an equivalent) have been used, especially in severe cases [10, 11]. Therefore, we initiated IV dexamethasone with an equivalent dose of 53.3 mg prednisolone (0.89 mg/kg/day prednisolone) immediately after the withdrawal of sulfasalazine. It is suggested that glucocorticoid should be continued until complete remission, and tapering its dosage should be performed gradually at least over 8 to 12 weeks [10, 12]. In this case, more than 50% reduction was considered following the partial improvement in the manifestations of drug reaction. The exacerbation occurred following rapid dose reduction; therefore, the patient was switched back to the previous IV dose and the complications were resolved. It is recommended that other

offending medications for the development of DRESS syndrome be avoided in an acute phase of this drug reaction to prevent exacerbation [13, 14].

Our patient only received IV dexamethasone, oral hydroxyzine, and topical glucocorticoid during hospitalization. However, following the approximate complete remission, the patient received IV visipaque® (iodixanol) as contrast media for CT angiography. The cutaneous manifestations of the DRESS syndrome along with dyspnea were exacerbated immediately after drug administration; we had to increase the doses of dexamethasone and hydroxyzine to ameliorate skin and lung inflammation. It has been reported that iodixanol can cause delayed

hypersensitivity reaction with the presentation of maculopapular rashes and without the involvement of internal organs in approximately 0.4% of the patients [15]. However, to our best knowledge, we did not find any report of iodinated contrast media-induced DRESS syndrome in the literature.

It seems that patients suffering from DRESS syndrome are sensitive to the administration of other new medications that cause a high possibility of hypersensitive reactions, including the iodinated contrast media. Therefore, if possible, the administration of these types of medications should be limited to only necessary conditions [14].

To the best of the author's knowledge, this is the first reported case of sulfasalazine-induced DRESS syndrome, which was exacerbated by the iodinated contrast media. We conclude that this type of contrast media should be used cautiously in patients who are treated for DRESS syndrome.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. Written informed consent form was obtained from the patient.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors would like to thank Dr. Alijani for visiting the patient in hospital and all the nurses and the patient who cooperated in conducting this study.

References

- [1] Waseem D, Latief M, Sofi N, Dar I, Khan Q, Abbas F, et al. Dress syndrome: A review and update. *Skin Dis Skin Care*. 2016; 1(1):8. https://www.researchgate.net/profile/Waseem-Dar/publication/298485704_Dress_Syndrome_A_Review_and_Update/links/56e9abf208ae25ede830b1a0/Dress-Syndrome-A-Review-and-Update.pdf
- [2] Criado PR, Criado RF, Avancini JM, Santi CG. Drug reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug-induced Hypersensitivity Syndrome (DIHS): A review of current concepts. *Anais Brasileiros de Dermatologia*. 2012; 87(3):435-49. [DOI:10.1590/S0365-05962012000300013] [PMID]
- [3] Choudhary S, McLeod M, Torchia D, Romanelli P. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. *The Journal of Clinical and Aesthetic Dermatology*. 2013; 6(6):31-7. [PMID] [PMCID]
- [4] Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. *J Am Acad Dermatol*. 2013; 68(5):709.e1-9; quiz 718-20. [DOI:10.1016/j.jaad.2013.01.032] [PMID]
- [5] Kirchhof MG, Wong A, Dutz JP. Cyclosporine treatment of drug-induced hypersensitivity syndrome. *JAMA Dermatology*. 2016; 152(11):1254-7. [DOI:10.1001/jamadermatol.2016.2220] [PMID]
- [6] Singh JA, Saag KG, Bridges Jr SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care & Research*. 2016; 68(1):1-25. [DOI:10.1002/acr.22783] [PMID]
- [7] Cildag S, Senturk T. Sulfasalazine-related hypersensitivity reactions in patients with Rheumatic diseases. *Journal of Clinical Rheumatology*. 2017; 23(2):77-9. [DOI:10.1097/RHU.0000000000000490] [PMID]
- [8] Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist?. *The British Journal of Dermatology*. 2007; 156(3):609-11. [DOI:10.1111/j.1365-2133.2006.07704.x] [PMID]
- [9] Roujeau JC, Allanore L, Liss Y, Mockenhaupt M. Severe Cutaneous Adverse Reactions to drugs (SCAR): Definitions, diagnostic criteria, genetic predisposition. *Dermatol Sinica*. 2009; 27(4):203-9. [DOI:10.1111/j.1365-2133.2006.07704.x]
- [10] Cho YT, Yang CW, Chu CY. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An interplay among drugs, viruses, and immune system. *International Journal of Molecular Sciences*. 2017; 18(6):1243. [DOI:10.3390/ijms18061243] [PMID] [PMCID]
- [11] Funck-Brentano E, Duong TA, Bouvresse S, Bagot M, Wolkenstein P, Roujeau JC, et al. Therapeutic management of DRESS: A retrospective

- study of 38 cases. *Journal of the American Academy of Dermatology*. 2015; 72(2):246-52. [DOI:10.1016/j.jaad.2014.10.032] [PMID]
- [12] Shiohara T, Kano Y, Hirahara K, Aoyama Y. Prediction and management of drug reaction with eosinophilia and systemic symptoms (DRESS). *Expert Opinion on Drug Metabolism & Toxicology*. 2017; 13(7):701-4. [DOI:10.1080/17425255.2017.1297422] [PMID]
- [13] Taghvaye Masoumi H, Hadjibabaie M, Zarif-Yeganeh M, Arasteh O. Exacerbation of allopurinol-induced drug reaction with eosinophilia and systemic symptoms by teicoplanin: A case report. *Journal of Clinical Pharmacy and Therapeutics*. 2017; 42(5):642-5. [DOI:10.1111/jcpt.12556] [PMID]
- [14] Picard D, Vellar M, Janela B, Roussel A, Joly P, Musette P. Recurrence of drug-induced reactions in DRESS patients. *Journal of the European Academy of Dermatology and Venereology*. 2015; 29(4):801-4. [DOI:10.1111/jdv.12419] [PMID]
- [15] Häussler MD. Safety and patient comfort with iodixanol: A post-marketing surveillance study in 9515 patients undergoing diagnostic CT examinations. *Acta Radiologica*. 2010; 51(8):924-33. [DOI:10.3109/02841851.2010.504739] [PMID]