International Journal of Advances in Medicine
Priyadarshini I et al. Int J Adv Med. 2024 Mar;11(2):130-134
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20240365

Case Report

An observed repeat case of drug reaction with eosinophilia and systemic symptoms syndrome with modified anti-tuberculosis therapy: a case report

Indu Priyadarshini[1]*, Akhilesh Thole[2], Kapil Hazarika[1], Manik S. Ghadlinge[1]

[1]Department of Pharmacology, ABVIMS and Dr. RML Hospital, New Delhi, India
[2]Department of Dermatology, ABVIMS and Dr. RML Hospital, New Delhi, India

Received: 28 December 2023
Accepted: 31 January 2024

***Correspondence:**
Dr. Indu Priyadarshini,
E-mail: ipriyadarshini17@gmail.com

ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, while uncommon, presents a potentially hazardous condition. It is a drug-induced multi-system immunological hypersensitivity reaction, characterized by the triad of fever, rash, and internal organ involvement. This is a case report of a 60-year-old Indian female who developed a repeat episode of DRESS syndrome following modified anti-tuberculosis therapy (ATT). She had a past history of DRESS syndrome caused by first-line antitubercular drugs. This case report aims to highlight the challenges in managing DRESS syndrome in the context of tuberculosis (TB) treatment, as well as to emphasize the importance of prompt withdrawal of the culprit drugs and immediate initiation of appropriate supportive care. This case report also highlights the high risk of recurrence of DRESS syndrome following the re-administration of the offending medication, especially antitubercular drugs.

Keywords: DRESS syndrome, ATT, Modified ATT

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, while uncommon, presents a potentially hazardous condition. It is a drug-induced multi-system immunological hypersensitivity reaction, characterized by the clinical triad of fever, rash, and internal organ involvement.[1,2] Features include skin eruption, lymphadenopathy, internal organ involvement (liver, kidney, lung etc.) and hematologic abnormalities like eosinophilia and atypical lymphocytes.[3]

The manifestations of DRESS syndrome are often delayed with a long latency period. It may appear in 2-6 weeks after the initiation of drug therapy. It has a long duration of course with aggravation or persistence of the symptoms even after withdrawal of the culprit drug. The rate of mortality reported in DRESS syndrome is approximately 8-10%, as it involves multiple internal organs among which the liver is most common. It requires early recognition with prompt diagnosis and treatment.[4]

Different classes of drugs are responsible for the causation of DRESS syndrome among which the most common are carbamazepine, allopurinol, phenytoin, phenobarbital, lamotrigine, sulfasalazine, and vancomycin.[5,6] First- or second-line anti-tubercular (anti-TB) drugs have also been found to be associated with this clinical entity of DRESS syndrome.[2,7-9] Approximately 60% of TB patients experience some kind of adverse drug reaction during therapy. Adverse drug reactions caused by anti-TB drugs are the leading cause of treatment failure, and reduced drug compliance and thus may cause an increase in mortality and morbidity. It also increases the financial burden on patients along with their prolonged hospitalization, unscheduled outpatient visits, and additional diagnostic tests. However, if the responsible drugs are identified

accurately, TB could be managed effectively with alternative and safe anti-TB drugs.[8-10] Different studies reported that most of the patients with this syndrome recover completely in weeks to months after the withdrawal of the responsible drug.[2,8]

The pathological mechanism behind DRESS syndrome is not well known. The four first-line anti-TB drugs *viz* rifampicin, isoniazid, pyrazinamide, and ethambutol are administered concomitantly in the treatment of TB. This multidrug therapy promotes the possibility of developing multi drug hypersensitivity syndrome (MDHS) and it is defined as drug hypersensitivity reaction (DHR) to at least two chemically and pharmacologically distinct drugs.[11,12]

Some other mechanisms which are involved in its development include defects in the metabolism of drugs which may cause the formation of reactive metabolites and subsequent immune reactions. The pathological changes of disease and prolonged administration of drug interferes with immunological function and also causes reactivation of human herpes, including Epstein-Barr virus and human herpes virus-6 and 7.[13] The mainstay of treatment for patients with DRESS syndrome is the identification and withdrawal of the offending drug as soon as possible.[10]

CASE REPORT

A 60-year-old Indian female weighing 50 kg presented to the medical emergency with complaints of fever, chills, rigors, itchy red raised lesions all over the body and facial swelling for the past two days. Redness and itching were involving >90% of the body surface area (BSA). Rashes appeared on the face and extended to the upper limbs, trunk and lower limbs.

Past medical history revealed that the patient was a known case of diabetes and was on insulin since December 2021. Subsequently, she was diagnosed with pulmonary TB and was prescribed isoniazid (H) (5 mg/kg), rifampicin (R) (10 mg/kg), pyrazinamide(Z) (25 mg/kg) and ethambutol (E) (15 mg/kg) on 17th March 2022. After six weeks of the start of treatment, she developed severe itching and rash all over the body along with fever. Drug reaction due to anti-TB drugs was suspected and all the drugs were withdrawn on 3rd May 2022 by the physician. Symptoms were not resolved and the patient was admitted and managed conservatively in the medicine department of a tertiary care hospital. A skin biopsy of the lesions done was suggestive of lichenoid drug reaction. Tablet levofloxacin (Lfx) 750 mg once daily and inj. streptomycin (STM) 0.75 mg i/m once daily i.e. modified antitubercular therapy (ATT) administered along with tablet prednisolone during hospital stay. There was marked clinical and analytical improvement of the signs and symptoms, thus allowing slow tapering of corticosteroids. Isoniazid 300 mg was reintroduced and well tolerated by the patient. After complete recovery, she was discharged from the hospital and modified ATT (Lfx and STM) with isoniazid was prescribed.

After 22 days of discharge (5th June 2022), the patient presented again to the medical emergency with complaints of fever, chills, rigors, severe itching, rash all over the body and facial swelling.

On clinical examination, oral temperature 102.7°F, blood pressure 110/70 mmHg, pulse 90 beats per minute, respiratory rate 20 breaths per minute, and oxygen saturation 97.0% were recorded. On cutaneous examination, generalised erythema and desquamative scaling were present all over the body. Scales were coarse, semi-adherent and copious in amount. Fissuring was present over the soles and palms. Oral mucosa was normal. Subungual hyperkeratosis and onycholysis were present on nails.

Laboratory examinations showed a haemoglobin concentration of 12.7g/dL, leukocyte count of 6,800/mm^3 (neutrophils 75%, lymphocytes 12.0%, monocytes 1%, and eosinophils 12%), absolute eosinophil count was 2100/µL, indicative of eosinophilia. Liver function tests showed elevated levels of aspartate aminotransferase (AST) at 420 IU/L, alkaline aminotransferase (ALT) at 414 IU/L, alkaline phosphatase (ALP) at 174 IU/L, lactic dehydrogenase (LDH) at 634 IU/L, total protein at 5.8 g/dL, albumin level at 3.5 g/dL, and total bilirubin level at 1.1 mg/dL. Fasting blood sugar (FBS) was measured at 191 mg/dL, and serum creatinine level was 0.5 mg/dL. Serology tests for rk39 and malaria were negative. Ultrasonography of the abdomen revealed hepatomegaly, while the electrocardiogram showed a normal sinus rhythm.

Isoniazid was immediately discontinued. In addition to conservative treatment, the patient was prescribed oral prednisolone 50 mg once daily for 14 days, followed by a gradual tapering of the dose. Tablet montelukast (10 mg) + levocetirizine (5 mg) were administered twice daily, and a moisturizer along with white soft paraffin was applied locally twice daily.

Tablet Lfx and inj. STM were also withdrawn after admission. After two weeks of hospitalization, tablet cyclosporin 100 mg was initiated twice daily for 14 days, and tablet hydroxyzine 20 mg was administered three times daily. The dosage of cyclosporin was gradually tapered down after 14 days. Over the course of one month, the patient's skin lesions gradually resolved.

After the resolution of the skin lesions, inj. STM 0.75 mg intramuscularly and tablet Lfx 750 mg orally were reintroduced along with tablet linezolid 600 mg once a day. However, the patient experienced severe itching and skin exfoliation within four hours of receiving the STM injection. As a result, inj. STM 0.75 mg was discontinued, while tablet linezolid 600 mg once a day and tablet Lfx 750 mg once a day were continued in combination with tablet cyclosporin 50 mg for four weeks. The patient showed symptomatic improvement with the recovery of skin lesions within one week.

DISCUSSION

DRESS syndrome typically manifests within 8 weeks after initiating drug therapy. This syndrome is typically identified by skin rashes, fever, lymphadenopathy, and visceral organ involvement, especially liver. Approximated mortality rate associated with it is around 8-10% and is often attributed to infiltration of eosinophilic cells leading to extensive liver damage.[13,14]

To aid in the diagnosis, the RegiSCAR scoring system is employed. RegiSCAR is a European registry for severe cutaneous adverse reactions (SCAR), including DRESS syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis. This European registry for severe cutaneous adverse reactions scoring system classifies DRESS cases as "no," "possible," "probable," or "definite".

All suspected cases with a score of 6 and above are categorized within definite classes, scores of 4 and 5 are categorized under probable cases, while scores of 2 and 3 suggest possible cases, and scores below 2 reject the diagnosis of DRESS syndrome.[6,8,15]

Table 1: RegiSCAR score for DRESS.

RegiSCAR score		-1	0	+1	2	Clinical case
Fever > 38ºC		No/U	Yes			0
Enlarged lymph nodes			No/U	Yes		0
Eosinophils			No/U	700-1499/L	>1500/L	2
Atypical lymphocytes			No/U	Yes		0
Skin involvement						
Skin rash extent (% body surface area)			No/U	>50%		1
Skin rash suggesting DRESS		No	U	Yes		1
Suggestive DRESS biopsy		No	Yes/U			0
Organ involvement*	Liver		No	Yes		1
	Kidney		No	Yes		0
	Pancreas		No	Yes		0
	Others		No	Yes		0
Resolution ≥ to 15 days		No/U	Yes			1
Evaluation of other potential causes: ANA, blood culture, serology for HAV, HBV, HCV, chlamydia, mycoplasmas. If none positive and ≥ of 3 above negatives				Yes		1
Total clinical case points						7

*After exclusion of other explanations: 1-one organ; 2- two or more organs. HAV-Hepatitis A virus; HBV-Hepatitis B virus; HCV-Hepatitis C virus; ANA-Antinuclear antibody. U-Unknown/unclassifiable and unlikely case: 2 points, probable case: 3-5 points, Final case: ≥6 points.

As per RegiSCAR scoring system, in this case study, score is more than 6 (total score of 7), hence the diagnosis strongly supports a definite case of DRESS syndrome (Table 1).

Prompt discontinuation of the causative drug and prescribing systemic corticosteroids is considered the mainstay of the treatment for DRESS syndrome.[16] Oral antihistamines are commonly used for other prominent symptoms such as pruritus, urticaria, skin eruptions, erythema nodosum and maculopapular exanthema. It is noticed that following the withdrawal of offending drugs, most of the cases of DRESS syndrome completely recover within weeks to months.[10] Severe adverse reactions to anti-tubercular drugs, including ethambutol or streptomycin-induced DRESS syndrome, as well as rifampicin or pyrazinamide-induced vasculitis were documented by several published case reports.[2,7,9,10,12]

The pathogenic mechanism of DRESS syndrome is not completely understood and it seems to be most likely multifactorial in origin. The most common proposed mechanisms for the origin of dress syndrome include alteration in drug metabolism which may lead to the generation of harmful reactive metabolites and subsequent immune- induced reactions, slow acetylation, and reactivation of human herpesviruses namely Epstein-Barr virus and human herpesvirus (HHV)-6 and-7.[13,17] Patch tests can be useful for detecting non-immediate drug reactions, however, the sensitivity of these drugs varies depending on the vehicle and drugs tested.[9,18] The gold standard method for the identification of the culprit drug is a drug re-challenge test, where re-exposure to the same drug leads to a recurrence of severe symptoms.[9,19]

In this case report, we observed that modification in the anti-TB drug regimen induces a recurrence of DRESS syndrome. The patient developed DRESS syndrome symptoms after initiation of first-line anti-tubercular drug therapy, including rifampicin, isoniazid, pyrazinamide, and ethambutol. After the conformation of DRESS syndrome by skin biopsy all the first-line drugs were discontinued, and corticosteroid therapy was initiated.

After the withdrawal of the offending drugs, the patient experienced a fast recovery. The re-challenge with isoniazid was also performed, and the patient tolerated it very well. However, within a few days of discharging from the hospital, the patient again presented to the medical emergency with severe symptoms of DRESS syndrome which includes fever, skin rashes and facial swelling. At the time of presentation in medical emergency, the patient was on modified anti-TB treatment consisting of inj. STM, tablet isoniazid, and tablet Lfx.

The anti-tubercular treatment was discontinued once again, and the patient was put on aggressive management with steroids and cyclosporin. Later, the patient was discharged with tablet linezolid and tablet Levofloxacin.

CONCLUSION

This case report emphasizes the importance of vigilance for DRESS syndrome in patients, who are receiving ATT. Upon re-administration of the offending medication, the risk of DRESS syndrome recurrence elevated significantly. Therefore, it is crucial for attending clinicians who are prescribing anti-TB drugs to exercise caution, remain vigilant regarding the potential for this severe hypersensitivity reaction to occur and promptly recognize the clinical manifestations. Prompt withdrawal of the culprit drugs and immediate initiation of appropriate supportive care, including systemic corticosteroids, can improve patient outcomes. In the future, further research and increased awareness about this rare but serious condition are warranted to optimize the management of DRESS syndrome in patients who are undergoing the treatment of TB. The role of systemic corticosteroids in the treatment of DRESS syndrome and monitoring of organ involvement should also be considered.

ACKNOWLEDGEMENTS

Author would like to head of the department of dermatology and nursing staff members and data entry operators. Also, head of the department of pharmacology for their support and encouragement.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. James J, Sammour YM, Virata AR, Nordin TA, Dumic I. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Secondary to Furosemide: Case Report and Review of Literature. Am J Case Rep. 2018;19:163-70.
2. Kaswala DH. Drug Rash with Eosinophilia and Systemic Symptoms Syndrome Due to Anti-TB Medication. J Family Med Prim Care. 2013;2(1):83-5.
3. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg. 1996;15(4):250-7.
4. De A, Rajagopalan M, Sarda A, Das S, Biswas P. Drug Reaction with Eosinophilia and Systemic Symptoms: An Update and Review of Recent Literature. Indian J Dermatol. 2018;63(1):30-40.
5. Stirton H, Shear NH, Dodiuk-Gad RP. Drug Reaction with Eosinophilia and Systemic Symptoms (DReSS)/Drug-Induced Hypersensitivity Syndrome (DiHS)-Readdressing the DReSS. Biomedicine. 2022;10(5):999.
6. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L et al. The DRESS Syndrome: A Literature Review. Am J Med. 2011;124(7):588-97.
7. Palmero D, Castagnino J, Musella RM, Mosca C, González Montaner P, De Casado GC. Difficult clinical management of anti-tuberculosis DRESS syndrome. Int J Tuberc Lung Dis. 2013;17(1):76-8.
8. Jung HY, Park S, Shin B, Lee JH, Lee SJ, Lee MK et al. Prevalence and Clinical Features of Drug Reactions with Eosinophilia and Systemic Symptoms Syndrome Caused by Antituberculosis Drugs: A Retrospective Cohort Study. Allergy Asthma Immunol Res. 2019;11(1):90-103.
9. Coster A, Aerts O, Herman A, Marot L, Horst N, Kenyon C et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome caused by first-line antituberculosis drugs: Two case reports and a review of the literature. Contact Dermatitis. 2019;81(5):325-31.
10. Lehloenya RJ, Dheda K. Cutaneous adverse drug reactions to anti-tuberculosis drugs: state of the art and into the future. Expert Rev Anti Infect Ther. 2012;10(4):475-86.
11. Sim DW, You HS, Yu JE, Koh YI. High occurrence of simultaneous multiple-drug hypersensitivity syndrome induced by first-line anti-tuberculosis drugs. World Allergy Organ J. 2021;14(7).
12. Carneiro-Leão L, Gomes I, Freitas C, Costa E Silva M, Viseu R et al. Multiple Drug Hypersensitivity Syndrome to Antituberculosis Drugs: A Case Report. J Investig Allergol Clin Immunol. 2020;30(1):70-1.
13. Lee JY, Seol YJ, Shin DW, Kim DY, Chun HW, Kim BY et al. A Case of the Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) Following Isoniazid Treatment. Tuberc Respir Dis (Seoul). 2015;78(1):27-30.
14. Fleming P, Marik PE. The DRESS syndrome: the great clinical mimicker. Pharmacotherapy. 2011;31(3):332.
15. Sasidharanpillai S, Ajithkumar K, Jishna P, Khader A, Anagha KV, Binitha MP et al. RegiSCAR DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) Validation Scoring System and Japanese Consensus Group Criteria for Atypical Drug-Induced Hypersensitivity Syndrome (DiHS): A Comparative Analysis. Indian Dermatol Online J. 2022;13(1):40-5.

16. Kim JH, Jang S, Kim D, Park S, Kim DG, Jung KS. A case of DRESS syndrome induced by the antituberculosis drugs, prothionamide, and para-aminosalycilic acid. Ann Allergy Asthma Immunol. 2013;110:118-9.
17. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transl Med. 2010;2(46):46ra62.
18. Romano A, Viola M, Gaeta F, Rumi G, Maggioletti M. Patch Testing in Non-Immediate Drug Eruptions. Allergy Asthma Clin Immunol. 2008;4(2):66-74.
19. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome. In vitro assessment of risk. J Clin Invest. 1988;82(6):1826-32.

Cite this article as: Priyadarshini I, Thole A, Hazarika K, Ghadlinge MS. An observed repeat case of DRESS syndrome with modified anti-tuberculosis therapy-a case report. Int J Adv Med 2024;11:130-4.