JoTH Journal of Tropical Health

Case Report

Leflunomide-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) - A Case Report

Sathiesha Padmasiri[1*], Ibrahim Mujahieth[2]

[1]Postgraduate Institute of Medicine, University of Colombo, Sri Lanka.
[2]Colombo South Teaching Hospital, Kalubowila, Sri Lanka.

Abstract

It is of paramount importance to identify a case of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) as it's potentially life-threatening. Although initially and commonly reported with anticonvulsants, the list of potential causative agents for DRESS has substantially widened over the years. We present a patient with a novel case of DRESS due to the use of leflunomide, which was successfully managed with prompt cessation of the drug and timely commencement of steroids. Leflunomide, widely used as an immunomodulatory agent in rheumatoid arthritis, has a long half-life, which leads to a prolonged course of DRESS in this case.

Keywords: DRESS, eosinophilia, lymphadenopathy, leflunomide

Funding: None
Competing interests: None
Received: 02 April 2025 **Accepted:** 31 May 2025 **Published:** 30 June 2025

***Corresponding author:** sathiesha123@gmail.com https://orcid.org/0000-0002-1894-972X

Cite this article as: Padmasiri S et al. Leflunomide-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) - A Case Report. Journal of Tropical Health 2025;1 (2): 119-123. DOI: http://doi.org/10.4038/joth.v1i2.13

Introduction

DRESS syndrome is a severe, drug-induced, idiosyncratic multisystem reaction [1]. It is characterised by fever, skin rash, lymphadenopathy, haematological abnormalities, and internal organ involvement [2]. In 2007, The European Registry of Severe Cutaneous Adverse Reactions (Regis CAR) introduced a diagnostic scoring system [3]. Leflunomide, a disease-modifying antirheumatic drug (DMARD), has been very rarely reported as a cause of DRESS syndrome. In contrast, drugs like hydroxychloroquine and sulfasalazine have been commonly implicated in the development of DRESS [4]. We report a rare case of a woman aged 47 years who presented to our hospital with a history of leflunomide usage and symptoms of DRESS. This case study highlights the potential risk of leflunomide in causing DRESS syndrome and the importance of active vigilance for drug eruptions when a patient presents with fever, rash, lymphadenopathy and organ involvement.

Case Presentation

We report a 47-year-old woman presenting with an itchy maculopapular rash for 8 days, fever and generalised body malaise. The rash initially appeared on the thighs and later progressed to the legs and trunk. The patient denied any contact history of rash and fever. Upon further questioning, it was revealed that she has been suffering from multiple joint pains and aches for a few years, and she was started on leflunomide by a rheumatologist for a diagnosis of seronegative rheumatoid arthritis 4 weeks back. She tested negative for rheumatoid factor and anti-citrullinated cyclic peptide (anti-CCP) antibodies.

On day 1 of the presentation, the patient was noted to be having a high spike of fever and right hypochondriac pain. Upon examination, she was icteric but not pale. A few shotty level II cervical lymph nodes were noted, and she also had a right-sided enlarged inguinal lymph node. The morbilliform rash was widely distributed on the bilateral arms, legs, chest, and torso. **(Figure 1).** Upon examination, her blood pressure was 110/78 mmHg, and her pulse rate was 100 beats per minute. She had right hypochondrial tenderness on abdominal examination.

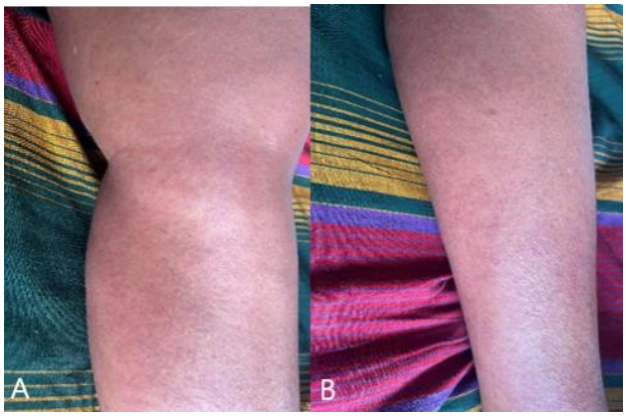

Image 1: A and B-Morbilliform rash observed in the lower limbs

During this period, Sri Lanka experienced a rise in measles cases, which were initially suspected as the diagnosis, but investigations led to an unexpected diagnosis. The investigation summary is shown in Table 1. The blood picture showed mild leukocytosis with lymphocytosis, moderate eosinophilia, several reactive lymphocytes, and few plasmacytoid lymphocytes. (plasmacytoid= atypical) Ultrasound scan of the abdomen showed no evidence of cholangitis, with the liver showing a mild coarse echo pattern that was suggestive of hepatitis.

The marked finding was the eosinophilia of 25 % ($5.39x10^9$) in this patient, which directed us towards the suspicion of DRESS. The criteria for this system include: first, fever greater than 38.5°C; second, enlarged lymph nodes; third, eosinophilia; fourth, atypical lymphocytosis; fifth, skin involvement; sixth, organ involvement. As the above few criteria were fulfilled, the diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome was established. Our patient fulfilled 8 points in the RegiSCAR criteria. The only culprit drugs identified were leflunomide, as she was started on this recently, and she denied the use of any other offending drugs. Leflunomide was immediately discontinued, and the patient was started on oral prednisolone at the dose of 1 mg/kg/day for 2 weeks, which tapered over the next 8 weeks. The patient exhibited a rapid resolution of fever, eosinophilia, and a progressive improvement in the skin rash; however, liver dysfunction persisted for 8 weeks before resolving. RegiSCAR criteria for DRESS also include the resolution of symptoms delayed for more than 15 days after discontinuation of the drug. This patient was kept in the ward for 14 days, and the rash was slowly subsiding, with a much slower decline in liver enzymes. She was reviewed with repeat FBC and liver function tests at 3 weeks and 4 weeks, respectively, and it showed gradual normalisation of liver enzymes. The primary differential diagnoses included septicaemia, autoimmune diseases including vasculitis, adult-onset Still's disease, tick-borne diseases, and viral disease, including viral hepatitis. These conditions were excluded by clinical history and relevant serological investigations. The plausible alternative diagnosis of viral exanthema was excluded by negative Epstein–Barr virus (EBV) antibodies, negative monospot tests and negative cytomegalovirus (CMV) PCR. Hepatitis A IgM levels, Hepatitis B surface antigen, and Hepatitis viral studies were all negative. Serum ferritin was normal, excluding adult-onset still's disease. Measles IGM and ANA tests were negative. The rickettsial antibodies tested using an immunofluorescent assay were negative, ruling out rickettsial infection as a cause of the rash and fever. This patient scored 7 points in the REGISCAR criteria, which tallied with the definite diagnosis of DRESS syndrome.

Discussion

We hereby report a case of DRESS induced by leflunomide, successfully managed with prompt cessation of the offending drug and timely initiation of steroids. Our case fulfilled 7 points of the REGISCAR criteria, including fever, enlarged lymph nodes, presence of atypical lymph nodes, eosinophilia, skin rash, involvement of two organs (both liver and kidneys), and resolution of the injury taking more than 15 days.

There have been several antiepileptic, antibiotics and sulphur-containing drugs widely associated with DRESS syndrome. However, leflunomide is very rarely associated with DRESS as there have only been a few cases, to our knowledge, that have been documented thus far [4]. The diagnostic criteria for DRESS have been developed based on clinical and laboratory abnormalities. The original criteria were proposed by Bocquet et al. in 1996 [5]. It has also expanded to two additional commonly used diagnostic criteria: the RegiSCAR and the J-SCAR [5]. The RegisCAR group has inclusion criteria for hospitalised patients suspected

to have DRESS, consisting of at least 3 of the following systemic features developing weeks to months after drug initiation: acute skin rash, fever greater than 38°C, lymphadenopathy, internal organ involvement, and hematologic abnormalities, including atypical lymphocytosis, eosinophilia, and thrombocytopenia. If a case is included based on those criteria, a further scoring system is applied to classify the case as an excluded, possible, probable, or definite case of DRESS. Based on the RegiSCAR score, DRESS can be classified as no case (score < 2), possible (score 2–3), probable (score 4–5), and definitive (score >6).

Table 1: Laboratory investigation results at presentation and variation throughout the illness

Test	Value DAY 1	DAY 10	Day 30	DAY 60	Reference ranges
White blood cell count	16.21	15.85	11.45	12.62	4-10x10^9/L
Eosinophils (%)	3.34 (20.6%)	6.06 (38.3%)	N/A	0.35 (2.5%)	0.02-0.5x10^9/L (0.5-5%)
Platelets	365	334	290	410	150-400x10^9/L
Haemoglobin	12.2	11.5	N/A	11.2	11-16g/dL
Erythrocyte Sedimentation Rate	60	N/A	N/A	14	<10mm/hour
Aspartate aminotransferase (AST)	128	188	110	18.3	<50U/L
Alanine aminotransferase (ALT)	219	256	178	40.3	<50U/L
Gamma glutamyl transferase	916	456	358	110	<55U/L
Alkaline phosphatase	534	429	267	122.5	40-150U/L
Total bilirubin	35.5	40.7	31.4	18.0	5-21µ/mol/l
Direct bilirubin	25.7	30.2	23.2	6.0	0-3.4 µ/mol/l
Serum creatinine	70.9	70.4	70	68	74-110µ/mol/L
Sodium	134	136	135	139	136-146 mmol/l
Potassium	4.2	4.5	4.3	3.7	3.5 -5.1mmol/l
C reactive protein	28.2	N/A	N/A	N/A	<5mg/L

The Naranjo Algorithm, also known as the Adverse Drug Reaction Probability Scale, is a method for assessing the causal relationship between an identified untoward clinical event and a drug, using a simple questionnaire to assign probability scores [6]. A timeline was created to establish a relationship between the initiation of leflunomide and the sequence of adverse events. In our case, the Naranjo scale yielded a total score of 6, pointing towards the probable adverse drug reaction. Although the pathogenesis of DRESS is still being investigated, two competing hypotheses aim to explain the syndrome. One hypothesis is that DRESS syndrome occurs through a delayed hypersensitivity reaction whereby CD4 and CD8 T cells are specifically activated by the offending drug to overproduce cytokines and acute phase reactants [7]. Another theory suggests that the offending agent triggers the activation of underlying HHV6, HHV7, EBV or CMV, and the ensuing symptoms are secondary to the body's immune system responding to the virus. Our patient presented with generalised rash, fever and systemic disorders such as severe eosinophilia, liver involvement and renal involvement.

In the management of DRESS, it is of great importance to recognise the signs of stigmata and immediately discontinue the drug. The key issue with DRESS syndrome is that the rash does not simply resolve with discontinuation of the drug; systemic corticosteroids (prednisone 0.5–1 mg/kg/d) and monitoring of laboratory tests for visceral involvement are indicated. The most common organ to be involved in DRESS syndrome is the liver [7], and mortality for the syndrome is approximately 10%, especially in patients with severe multi-organ involvement. In our case, the liver was the organ primarily affected. Additionally, our patient exhibited proteinuria of 3+ in the urine full report, with transient sub-nephrotic range proteinuria and normal serum creatinine and eGFR. Proteinuria with or without acute kidney injury is a marker of renal injury in DRESS. A report published by Da Silva et al. of Brazil has reviewed case reports in which patients had renal injury during the episode of DRESS syndrome. Only 4% of patients had isolated proteinuria during the episode of DRESS without AKI [8]. This phenomenon was seen in our patient. The repeated urine full report after one month had protein trace only with timely cessation of leflunomide and initiation of steroids. Ultimately, our patient had two organs

involved during the episode. With regards to liver injury in DRESS, it could range from a mild increase of liver enzymes to acute fulminant hepatic failure, with the cholestatic type as the most common pattern [9,10]. Our patient, too, had a cholestatic pattern of liver injury, as the R factor was 1.2. It took nearly two months for the liver enzymes to return to normal.

Although widely used in clinical practice, the use of systemic corticosteroids for treating DRESS has not been studied in randomised trials; however, it is currently the most accepted treatment. Its early administration is recommended for almost all cases of DRESS, and the dose should start at a minimum of 1 mg/kg/day of prednisolone. Gradual tapering should be done over 3 to 6 months to minimise the risk of relapse. Thus, our patient was also started on a prednisolone tapering regimen and continued for 3 months and gradually tailed off. Our patient took almost 2 months to recover from DRESS, potentially due to the long half-life of leflunomide. Leflunomide is highly protein bound with a half-life of 15-16 days.

Out of the antirheumatic drugs used widely worldwide, hydroxychloroquine and sulfasalazine are very well known to cause DRESS syndrome. However, cases of DRESS associated with leflunomide are rare. India has reported a few cases of DRESS syndrome associated with leflunomide use. A case report published in Pakistan by Fatima M et al. has highlighted a case of atypical DRESS associated with leflunomide [11]. Table 2 summarises the published cases of leflunomide-induced DRESS syndrome. Our case report can be considered as the first reported case of DRESS syndrome with the use of Leflunomide in Sri Lanka. DRESS mostly carries a favourable prognosis. Early recognition of DRESS is vital to ensure that the inciting drug is discontinued and supportive treatment is started immediately.

Table 2: Patient demographics of the DRESS syndrome due to leflunomide

Author(s)	Year	Journal	Patient Demographics	Key Details
Parajuli S et al. [1]	2012	Nepal Journal of Dermatology, Venereology & Leprology	40-year-old female from Nepal with rheumatoid arthritis	Developed DRESS syndrome 5 days after starting leflunomide; presented with exfoliative dermatitis, fever, lymphadenopathy, and organ dysfunction; died after 3 months despite treatment.
Fatima M et al. [11]	2023	Mediterranean Journal of Rheumatology	32-year-old female from India with rheumatoid arthritis	Developed DRESS syndrome 20 days after starting leflunomide; presented with maculopapular rash, fever, eosinophilia, and liver involvement; managed with steroids.

Conclusion

DRESS is potentially a life-threatening adverse drug reaction with adverse effects mainly on the kidneys and liver. Prompt diagnosis, withdrawal of the offending drugs and timely commencement of steroids are cornerstones of the management. Leflunomide, a new immunomodulatory drug, being highly protein bound with a long half-life, can be associated with prolonged DRESS syndrome. Fever, lymphadenopathy and rash should always raise the suspicion of DRESS. Long-term follow-up is necessary, as there is a risk of recurrence of DRESS.

Consent

Informed written consent was obtained from the patient for the publication of the case report and the images.

References

1. Choudhary S, McLeod M, Torchia D, Romanelli P. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. J Clin Aesthet Dermatol. 2013;6(6):31-7.

2. Maqbool S, Hsieh F, McDonnell J, Vasas D, Lang D. Safety and efficacy of omalizumab in atopic dermatitis; A preliminary report. J Allergy Clin Immunol. 2005;115(2):S106.
Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674904036917

3. Sasidharanpillai S, Ajithkumar K, Jishna P, Khader A, Anagha K, Binitha M, 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. doi: 10.4103/idoj.idoj_196_21.

4. Rao S, Sunkara A, Srivastava N, Sampat P, Ramos C, Albert E. An uncommon presentation of DRESS syndrome secondary to leflunomide use: a case report. J Investig Med High Impact Case Rep. 2021;9:232470962199728. doi:10.1177/2324709621997282.

5. Pannu A, Saroch A. Diagnostic criteria for drug rash and eosinophilia with systemic symptoms. J Fam Med Prim Care. 2017;6(3):693. doi:10.4103/2249-4863.222050.

6. Gupta S, Deep R, Khandelwal SK, Khaitan BK, Nishanth KN. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome in a patient with bipolar disorder: a case report. Indian J Psychol Med. 2021;43(3):269-70. doi:10.1177/0253717621989209.

7. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): an interplay among drugs, viruses, and immune system. Int J Mol Sci. 2017;18(6):1243. doi:10.3390/ijms18061243

8. Dagnon Da Silva M, Domingues SM, Oluic S, Radovanovic M, Kodela P, Nordin T, et al. Renal manifestations of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review of 71 cases. J Clin Med. 2023;12(14):4576. doi:10.3390/jcm12144576.

9. Martinez-Cabriales SA, Shear NH, Gonzalez-Moreno EI. Liver involvement in the drug reaction, eosinophilia, and systemic symptoms syndrome. World J Clin Cases. 2019;7(6):705-16. doi:10.12998/wjcc.v7.i6.705.

10. Chen K, Lin I, Yang H, Chu C. Clinical pattern of liver injury in drug reaction with eosinophilia and systemic symptoms (DRESS): a retrospective study in Taiwan. Clin Transl Allergy. 2014;4(S3):P18. doi:10.1186/2045-7022-4-S3-P18.

11. Fatima M, Azimi SS, Ashwini S, Radhakrishna MH. Leflunomide-induced atypical DRESS: a case report and literature review. Mediterr J Rheumatol. 2023;34(1):91. doi:10.31138/mjr.34.1.91.