



## Levetiracetam-induced dress syndrome in an elderly patient: a rare but serious adverse reaction

Dr. Ramkumar L Maddapur<sup>1\*</sup>, Dr. Tasmiya M Pathan<sup>2</sup>, Vivek Ramesh Gokhale<sup>2</sup>, Aishwarya siddamallanagoudpatil<sup>2</sup>,  
Dr. Ajay R<sup>3</sup>

<sup>1</sup> Lecturer, Department Pharmacy, BVVS HSK College of Pharmacy Bagalkote, Karnataka, India

<sup>2</sup> Department of Pharmacy, BVVS HSK College of Pharmacy Bagalkote, Karnataka, India

<sup>3</sup> Intern, Department of Pharmacy, Bapuji college of pharmacy, Davanagere, Karnataka, India

### Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is an uncommon but serious adverse drug reaction that can affect multiple organs and become life-threatening if not identified in time. It typically develops within 2 to 8 weeks of starting the offending drug, most often certain antiepileptic medications such as phenytoin or carbamazepine. Levetiracetam, although considered a safer alternative among antiepileptic, has only rarely been linked to DRESS. We describe the case of a 78-year-old woman with a background of cerebrovascular accident and a recently diagnosed seizure disorder, which was started on levetiracetam. Four weeks into therapy, she developed high-grade fever, altered mental status, and widespread fluid-filled skin lesions. Blood tests showed elevated Eosinophils counts, anemia, increased inflammatory markers, and worsening renal function. A Tzanck smear ruled out autoimmune blistering diseases. Based on clinical findings and RegiSCAR scoring, a diagnosis of DRESS was established. Levetiracetam was discontinued immediately, and the patient was treated with corticosteroids and supportive care, leading to steady clinical improvement. This case highlights the need to remain vigilant for DRESS, even with drugs that are typically well-tolerated. Early recognition and withdrawal of the causative drug are essential to prevent serious complications and improve recovery outcomes.

**Keywords:** Dress syndrome, Adr, Levetiracetam, RegiSCAR, elderly

### Introduction

Levetiracetam is a frequent treatment for partial-onset seizures and is a member of the anticonvulsant drug family. In 1999, levetiracetam received approval for use in medicine in the US. For patients one month of age and up, it is authorized for use as a combination treatment as well as a monotherapy [1]. It is also recommended as an adjuvant therapy for generalized seizures in adults and adolescents, including those associated with juvenile myoclonic epilepsy. Its association with synaptic vesicle protein 2A (SV2A), a membrane protein expressed on synaptic vesicles in the central nervous system, is primarily responsible for its therapeutic effects. It is thought that this interaction stabilizes neuronal activity by controlling the release of neurotransmitters [2]. A significant health concern is cutaneous adverse drug reactions (CADRs), which are side effects of drugs that affect the skin. Acute generalized exanthematous pustulosis, toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug response with eosinophilia and systemic symptoms (DRESS) are a few of these reactions, some of which can be quite dangerous. About 2% of all CADRs are severe responses, which must be promptly diagnosed in order to provide appropriate treatment and lower the risk of death [3]. Between 1 in 1000 and 1 in 10,000 drug exposures are likely to result in DRESS, a severe adverse drug-induced reaction [4]. The United States Food and Drug Administration (US FDA) advised of DRESS linked to antiseizure drugs like levetiracetam and clobazam on November 28, 2023 [5]. Levetiracetam is a widely used antiepileptic renowned for its good side-effect profile. Levetiracetam is an uncommon cause of DRESS, although DRESS is more common with other anticonvulsants [6]. A study of the FDA Adverse Event

Reporting System (FAERS) and the medical literature up until March 2023 revealed that levetiracetam was associated with 32 severe cases of DRESS globally [7].

The precise pathophysiology of DRESS is yet unknown. However, it is regarded as a T-cell-mediated delayed hypersensitivity reaction in which medications and their byproducts either serve as haptens or bind directly to T-cell receptors and/or human leucocyte antigens (HLA) to activate the immune system [8]. In order to assist doctors in proving or ruling out the diagnosis of DRESS, the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) suggested a score in 2007 [6].

### Case Study

A 78-year-old female presented with a four-day history of fever and one-day history of altered sensorium. The patient exhibited progressive tachycardia and reported the appearance of fluid-filled skin lesions distributed across the body. Her medical history was significant for a cerebrovascular accident (CVA) two years ago and a recently diagnosed seizure disorder for which she had been initiated on levetiracetam therapy two months prior. Approximately four weeks after the initiation of levetiracetam, the patient developed widespread fluid-filled cutaneous lesions. Local skin examination revealed multiple erythematous fluid-filled lesions and bullae over the bilateral upper limbs, lower limbs, chest, and abdominal wall.

Laboratory investigations showed a haemoglobin level of 10 g/dL and leucocytosis with a total WBC count of 15,100 cells/ $\mu$ L. Eosinophilia was noted with an 18% eosinophil count, suggestive of a T-cell-mediated hypersensitivity reaction characteristic of Drug Reaction with Eosinophilia

and Systemic Symptoms (DRESS) syndrome. Erythrocyte sedimentation rate (ESR) was elevated at 56 mm/hr, and procalcitonin was raised to 2.2 ng/mL, supporting the presence of a systemic inflammatory response. Renal function tests indicated elevated serum urea (56 mg/dL) and serum creatinine (1.6 mg/dL), while liver function tests revealed hyperbilirubinemia (Total bilirubin: 2.0 mg%, Direct bilirubin: 1.2 mg%), along with elevated liver enzymes (ALT: 41.4 U/L, AST: 64 U/L, ALP: 189.9 U/L), consistent with multi-organ involvement. To differentiate between bullous pemphigoid (BP) and DRESS, a Tzanck smear was performed. The smear was negative for acantholytic cells and showed a predominance of eosinophils, thereby ruling out BP and confirming the diagnosis of DRESS syndrome.

The patient’s clinical presentation was further evaluated using the RegiSCAR (Registry of Severe Cutaneous Adverse Reaction) scoring system for DRESS syndrome. The scoring criteria and their corresponding findings in this case were as follows:

**RegiSCAR Score for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [9].**

RegiscarScore for DRESS	No/Unknown	Yes
Fever (≥38.5 °C)	0	+1
Enlarged lymph nodes ≥2 sites, >1 cm	0	+1
Atypical lymphocytes	0	+1
Eosinophilia (10-19.9%)	0	+1
Skin rash extent >50%	0	+1
At least two of: edema, infiltration, purpura, scaling	0	+1
Biopsy suggesting DRESS	-1	0
Internal organ involved	0	+2
Resolution in ≥15 days	0	0
Alternative diagnoses excluded (by ≥3 biological investigations)	0	+1
<b>TOTAL</b>		<b>9</b>

According to the RegiSCAR classification, a score >5 confirms a definite case of DRESS syndrome.

Management involved immediate withdrawal of levetiracetam. The patient was initiated on prednisolone 20 mg twice daily for 7 days to control the hypersensitivity reaction. Fusidic acid was applied topically for skin lesions. Broad-spectrum antimicrobial therapy included linezolid, meropenem, and clindamycin, considering the elevated procalcitonin level and signs of secondary infection. Sodium valproate was introduced as an alternative anticonvulsant for seizure control. Given the patient’s history of cerebrovascular accident, Aspirin (75mg) + Atorvastatin (10mg) + Clopidogrel (75mg) was continued for antiplatelet support. Due to complaints of breathlessness, nebulization therapy was provided. Supportive care included administration of antiemetics, antacids, and RT (Ryle’s Tube) feeding every 3 hours for 5 days to ensure adequate nutrition.

Despite ongoing treatment and multidisciplinary management, the patient chose to discharge against medical advice (DAMA).

**Discussion**

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare, potentially life-threatening hypersensitivity reaction characterized by fever, skin rash, eosinophilia, and multiorgan involvement. Although classically associated with aromatic anticonvulsants such as phenytoin and carbamazepine, levetiracetam—generally regarded as a safer alternative—has also been rarely implicated [4]. In the present case, a 78-year-old female developed clinical features consistent with DRESS approximately four weeks after initiation of levetiracetam therapy, aligning with the typical latency period of 2–8 weeks. High-grade fever, altered sensorium, extensive cutaneous involvement, and systemic symptoms raised clinical suspicion. Diagnosis was confirmed based on laboratory parameters and dermatologic findings fulfilling the RegiSCAR criteria.

A similar case reported by Suzuki et al. described a 50 -year -old woman, who developed the DRESS three weeks after starting Levetiracetam, introduced with fever, rash and elevated liver enzymes. However, his position was comparatively unhappy, with no kidney involvement, and he was well recovered on corticosteroids alone without complications or prolonged hospitalization [10].

In addition, in a cohort study by Kardaun et al., Advanced age and many Comorbidities found correlated with more severe DRESS expressions and slow recovery, especially in cases with liver and kidney involvement [11]. Our patient also had a pre -history of cerebrovascular accident, hypertension, and on many drugs, which increased the possibility of hypersensitivity due to cumulative immune burden or drug interaction.

Advanced age changes can increase sensitivity to drug responses. Early recognition of aggressive agent and immediate withdrawal of aggressive agent is important in reducing sickness and mortality. Systematic corticosteroids remain the cornerstone of treatment and were associated with gradual clinical improvements in this case.



**Fig 1:** Cutaneous manifestations of DRESS syndrome over the gluteal region showing hyperpigmented maculopapular lesions with scaling, crusting, erosion, and post-inflammatory changes



**Fig 2:** Extensive upper limb involvement in DRESS syndrome showing erythematous, desquamating lesions with crusting, ulceration, and signs of secondary infection

10. Suzuki Y, Inoue H, Saito R, Inoue K, Komatsu H, Tsuboi Y. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome induced by levetiracetam.
11. Kardaun SH, Sekula P, Valeyrie-Allanore L, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol*.

### Conclusion

This report highlights the need for clinicians to maintain a high index of suspicion for DRESS, even with drugs like levetiracetam that are not commonly associated with hypersensitivity reactions. Close monitoring during the initial weeks of antiepileptic therapy, particularly in elderly patients, is essential for early detection and management of severe cutaneous adverse reactions.

### Reference

1. Levetiracetam: MedlinePlus Drug Information <https://medlineplus.gov/druginfo/meds/a699059.html>
2. Contreras-García JJ, Cárdenas-Rodríguez N, Romo-Mancillas A, Bandala C, Zamudio SR, Gómez-Manzo S, Hernández-Ochoa B, Mendoza-Torreblanca JG, Pichardo-Macias LA. Levetiracetam Mechanisms of Action: From Molecules to Systems. Pharmaceuticals (Basel).
3. Al About DM, Nessel TA, Hafsi W. Cutaneous Adverse Drug Reaction (CADR) [Internet]. PubMed. Treasure Island (FL): StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK533000/>
4. Dar WR, Sofi N, Latief M, Dar IA, Kasana BA. Levetiracetam-induced drug reaction with eosinophilia and systemic symptoms syndrome. *Indian J Dermatol*.
5. Maideen NMP, Kandasamy K, Balasubramanian R, Subramani AT. Drug reaction with eosinophilia and systemic symptoms (DRESS) associated with the use of antiseizure medications—An overview of clinical data. *Seizure: European Journal of Epilepsy*.
6. Leblanc M, Plaisance M. Levetiracetam-associated acute kidney injury and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *Open Journal of Nephrology*.
7. Brooks M. FDA Warns of Potentially Lethal Reaction to Seizure Meds [Internet]. Medscape. <https://www.medscape.com/viewarticle/998860>
8. Norman T, Guenther J, Wu K, DeClerck B, Worswick S. Vesiculopustular drug reaction with eosinophilia and systemic symptoms induced by levetiracetam. *Skin Health Dis*.
9. Ashok Kumar Pannu, Atul Saroch, Diagnostic criteria for drug rash and eosinophilia with systemic symptoms, *Journal of Family Medicine and Primary Care*.