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Clinical Letter

# A case of DRESS (drug reaction with eosinophilia and systemic symptoms) under treatment with eslicarbazepine

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## 1. Introduction

Adverse drug reactions (ADRs) are a well-known and often limiting problem in the pharmacological treatment of epilepsies. Cutaneous drug reactions – ranging from mild maculopapular exanthema (MPE) to severe Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN) are frequently observed in association with several antiepileptic drugs (AEDs) [1]. DRESS (drug reaction with eosinophilia and systemic symptoms) is a potentially life-threatening subtype that features hypereosinophilia, morbilliform skin eruptions, fever, facial edema, enlarged lymph nodes and other organ involvement and occurs with a latency of 2 to 6 weeks [2]. Cutaneous drug reactions occur predominantly in association with AEDs of the group of sodium channel blockers, comprising carbamazepine, oxcarbazepine, phenytoin and lamotrigine [1]. Several genetic polymorphisms have been identified as risk factors for cutaneous reactions with the most solid data for the HLA alleles HLA-B15:02 and HLA-A31:01 [3]. Beside anticonvulsants, DRESS had been described to be related to allopurinol and several antibiotics.

## 2. Case presentation

A 71-year-old man with structural epilepsy and refractory seizures was admitted to our hospital for adjustment of his medication plan. At the time of admission, he was treated with zonisamide (ZNS) 200 mg/d and perampanel (PER) 10 mg/d. The first seizures occurred five years before. His epilepsy syndrome was caused by a tumor in the left temporal lobe which was resected in the same year and was classified as diffuse astrocytic glioma (WHO II°). Follow-up magnetic resonance imaging (MRI) showed a stable course of disease. Repeated routine electro-encephalogram (EEG) showed epileptic discharges in the left fronto-temporal region. The patient continued to have focal impaired awareness seizures and bilateral tonic-clonic seizures and turned out to be pharmacoresistant to lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV) and valproic acid (VPA). Whilst on treatment with VPA a maculo-papular rash was reported on both arms. An epicutaneous patch test confirmed a type IV allergy to VPA. After a traumatic intracerebral hemorrhage in January 2018 he suffered from global aphasia and behavioral problems and was on treatment with risperidone 2,5 mg/d.

On admission, we changed the antiepileptic drug regime to eslicarbazepine (ESL), titrating from 400 mg to 1200 mg within 7 days, and continued PER 8 mg/d. ZNS was discontinued at once. 12 days after introduction of ESL, the patient developed morbilliform, confluent and generalized skin eruptions, predominantly of the neck, trunk and limbs (Fig. 1). This was followed by fever up to 40.3 °C, edema of face and neck and cervical lymphadenopathy 4 days later. Laboratory findings showed hypereosinophilia, anemia and elevated liver function tests (Table 1). Suspecting a bacterial infection at first, he was started on piperacillin/tazobactam and clarithromycin. Despite antibiotic treatment the fever continued. While C-reactive protein (CRP) was elevated, procalcitonin and leukocytes stayed within normal range. Under these circumstances, we suspected DRESS and started the patient on antihistamines and prednisolone. Prednisolone (250 mg) was once administered intravenously and then continued orally (1 mg/kg) for 10 days. ESL was stopped and antiepileptic treatment was changed to phenytoin (PHT) 200 mg/d and clobazame (CLB) 10 mg/d. Subsequently, fever, rash and lymphadenopathy diminished within few days. HLA-I-Testing revealed alleles A01, B07 and B08.

## 3. Discussion

Regarding differential diagnoses to DRESS, we considered other cutaneous drug reactions such as SJS/TEN and acute generalized exanthematous pustulosis (AGEP), viral infection, autoimmune disease, reactions to other drugs than ESL, and drug-drug interactions. SJS/TEN were unlikely due to the absence of erosive skin lesions and mucosal involvement and the presence of hypereosinophilia. AGEP was unlikely due to the long latency. Viral involvement could be possible as certain viral infections can mimic DRESS, e.g. Epstein-Barr Virus (EBV), cytomegalovirus (CMV), parvovirus B19, Dengue virus, or Coxsackie virus. Moreover, DRESS is associated with the reactivation of several viruses such as human herpes virus (HHV)-6, HHV-7 and EBV. The fact that the viral infection status was not assessed at the time of the patient's hospitalization presents a certain limitation for this case description. However, the presence of hypereosinophilia makes a viral infection as

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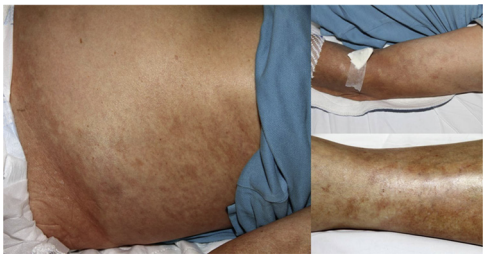

**Fig. 1.** Morbilliorm, confluent skin eruptions of the trunk, left arm and left leg 14 days after onset of symptoms.

**Table 1**
Laboratory findings.

| Variable | Reference Range[a], adults | 63 days before ESL | Day 23[b] | Day 26[b] | Day 42[b] | Unit |
|---|---|---|---|---|---|---|
| **Hemoglobine** | 14-18 | 11.70 | 9.70 | 7.10 | 10.00 | mg/dl |
| **Leucocytes** | 3.8-10.3 | 4.10 | 3.94 | 5.20 | 9.40 | 1000/µl |
| **Lymphozytes** | 1.1-3.2 | 0.96 | 0.55 | 0.45 | 0.40 | 1000/µl |
| **Neutrophiles** | 1.8-7 | 2.71 | 2.90 | 3.95 | 8.36 | 1000/µl |
| **Eosinophiles** | 0.03-0.47 | 0.07 | 0.32 | 0.64 | 0.04 | 1000/µl |
| **Thrombocytes** | 150-450 | 239 | 460 | 347 | 141 | 1000/µl |
| **LDH** | max 250 | 172 | 330 | 267 | 274 | U/l |
| **GOT** | max 50 | 11 | 78 | 63 | 52 | U/l |
| **GPT** | max 50 | 17 | 56 | 61 | 111 | U/l |
| **gGT** | max 60 | 20 | 126 | | 276 | U/l |

[a] Reference values are influenced many variables, as the patient population and the laboratory methods used. Ranges used at Uniklinikum Tübingen are for adults who are free of conditions that might affect the results.
[b] With beginning of ESL at Day 1.

the sole cause of the patient's syndrome unlikely. Autoimmune disease that could possibly mimic the symptoms, such as Kawasaki and Kikuchi-Fujimoto disease, were ruled out based on the patient's age and ethnicity. Reactions to other drugs could be possible, however the only change made to the patient's drug regime was the start of enoxaparin for thrombosis prevention, 10 days previous to the onset of symptoms. DRESS related to low-molecular-heparin is not known. DRESS has also been described in association with several antibiotics, inter alia, piperacillin and clarithromycin that were used in the present case. Since the antibiotics were started after the onset of symptoms a causal relation can be excluded. As for drug-drug interactions, CBZ and OXC cause a reduction of the PER plasma concentration. Contrariwise, PER may lead to a slight increase of OXC plasma concentration, whereas CBZ plasma concentration remains stable. We are not aware of any studies that compare ESL and PER explicitly. In our case, considering the related structure of ESL, CBZ, and OXC, a decrease of PER and an increase of ESL plasma concentration is possible. A rather brisk titration combined with a potential PER-triggered rise of ESL plasma concentration may have promoted the probability of DRESS.

We describe a single case of DRESS associated under ESL treatment. Further studies and a longer observation time for this still novel substance are certainly needed to corroborate our findings. However, we believe that this report can help to increase the awareness of clinicians for this possible adverse reaction when initiating treatment with ESL. Different aspects such as patient age, titration speed and potential drug interactions could possibly influence the likelihood of occurrence and should be closely monitored. In the future, testing for genetic risk factors could help to reduce the risk further.

## Declaration of Competing Interest

None

## Acknowledgements

The patient gave oral and written consent for the publication of his medical data and the photographs.

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