

# Probable drug-induced lupus erythematosus by zonisamide



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**Key words:** adult; antiepileptic drugs; drug reaction; drug-induced lupus erythematosus; seizure medication; zonisamide.

## INTRODUCTION

Antiepileptic drugs (AEDs) can lead to a rash at any time during treatment with a proposed incident rate of approximately 16%.<sup>1</sup> Drug-induced lupus erythematosus (DILE) represents approximately 10% of all systemic lupus cases in the United States with approximately 100 drugs being implicated.<sup>2</sup> DILE can present months to years after the start of a medication and resolves with discontinuation of the drug.<sup>3</sup> Many AEDs have been implicated in causing skin rashes with zonisamide, a sulfonamide derivative, showing an overall rash risk reported between 2% and 4%.<sup>1,4</sup> Zonisamide has been implicated in a photosensitive lichenoid drug eruption,<sup>5</sup> drug rash with eosinophilia and systemic symptoms,<sup>6</sup> toxic epidermal necrosis,<sup>7</sup> and systemic lupus erythematosus.<sup>8</sup> We report the second case of possible DILE from zonisamide, the first in an adult, to our knowledge.

## CASE REPORT

A 28-year-old Caucasian woman with a history of endometriosis underwent laparoscopic endometrial excision and ablation. One week following the surgical procedure, the patient had a tonic-clonic seizure. The evaluation in the emergency department and a neurology workup concluded with a diagnosis of juvenile myoclonic-absence epilepsy. The seizure trigger was attributed to the stress of surgery. No previous history of autoimmune disease was noted. Findings of the test for antinuclear

### Abbreviations used:

AED: antiepileptic drug  
ANA: antinuclear antibody  
DILE: drug-induced lupus erythematosus

antibodies (ANAs) were negative during the neurology workup.

The patient was started on zonisamide 200 mg with good control of her seizure activity. After approximately 6 months of therapy with zonisamide, symmetric, polycyclic lesions developed in the patient on sun-exposed areas beginning on the anterior aspects of her thighs and progressing to her chest and arms (Figs 1 and 2). No malar rash was seen on the face, and no fever or lymphadenopathy was noted. The arthralgias began approximately 2 weeks after the rash and worsened with time. A skin biopsy of the right arm was performed, which revealed prominent compact orthokeratosis, mild acanthosis, focal basal vacuolar changes, slight thickening of the basement membrane zone, and superficial and deep perivascular and periadnexal lymphocytic infiltrate with slightly increased dermal mucin consistent with a connective tissue disease such as lupus erythematosus (Figs 3 and 4). Findings of the ANA test were positive (1:1280) with a nuclear, speckled pattern (Quest Diagnostics). Specific antihistone testing was not performed. The patient was diagnosed with DILE secondary to zonisamide. Her medication was changed to levetiracetam 500 mg twice daily. No

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**Fig 1.** Symmetric, polycyclic lesions on the patient's chest.

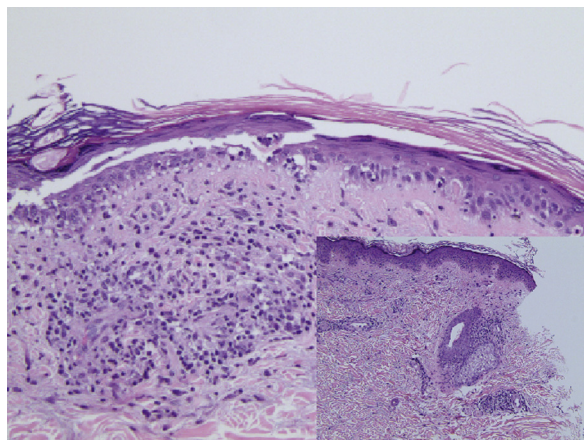


**Fig 2.** Symmetric, polycyclic lesions on the patient's right arm.

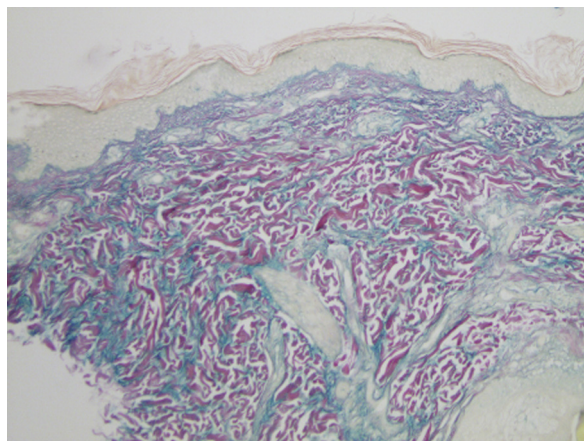
systemic or topical treatment was given for the skin lesions. After changing AED, within 3 weeks, her arthralgias resolved, and her skin lesions resolved with a remaining postinflammatory pigmentary change. A repeat ANA testing performed 4 weeks after discontinuing zonisamide was unchanged at 1:1280 with a nuclear, speckled pattern.

## DISCUSSION

AEDs that are capable of inducing DILE include carbamazepine, ethosuximide, phenytoin, diphenylhydantoin, primidone, trimethadione, valproate, and zonisamide.<sup>9</sup> Zonisamide is a synthetic 1,2-benzisoxazole-3-methanesulfonamide with anticonvulsant properties.<sup>7</sup> Skin rashes are reported in a small percentage of patients taking zonisamide.<sup>1,4</sup> Diagnostic guidelines for DILE include treatment with the suspected drug for at least 1 month, with symptoms including arthralgia, myalgia, fever, serositis, and rash with positive ANA test findings. Improvement in symptoms is usually seen within days to weeks of stopping the suspected drug.<sup>10</sup> DILE is typically characterized by positive ANA test



**Fig 3.** The skin biopsy from the upper portion of the right arm shows interface dermatitis with basal layer vacuolar change and occasional dyskeratotic keratinocytes. The lichenoid inflammatory infiltrate is composed of lymphocytes with extension along adnexa. (Hematoxylin-eosin stain; original magnifications:  $\times 200$ ; **inset**,  $\times 100$ .)



**Fig 4.** A colloidal iron special staining reveals increased interstitial dermal mucin. (Colloidal iron special stain; original magnification:  $\times 100$ .)

findings with a homogeneous pattern; however, a speckled ANA pattern may be seen.<sup>2</sup> Antihistone antibodies are found in 75% of patients with DILE; however, they are also found in 75% of patients with idiopathic lupus and, therefore, not specific for DILE.<sup>11</sup> The patient's sustained elevation in the ANA level is consistent with DILE, as the titer may not decrease for months or even years following the cessation of the offending medication.<sup>10</sup> Our patient had no previous history of autoimmune disease and had a photosensitive polycyclic rash without any malar involvement. The temporal sequence of events following therapy with zonisamide, with a photosensitive skin rash, arthralgias, and lack of a malar rash after 6 months of therapy with the

subsequent resolution of the arthralgias and skin lesions after discontinuing the medication, supports the diagnosis of DILE from zonisamide.

#### Conflicts of interest

None disclosed.

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