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Authors

Bhatti, Safiyyah A
Joffe, Daniel
Webster, Timothy
et al.

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Drug-induced subacute cutaneous lupus erythematous from cenobamate: case presentation and review of the literature

Safiyyah A Bhatti[1,2] MD, Daniel Joffe[1] BS, Timothy Webster[1] MD, Jason B Lee[1] MD, Neda Nikbakht[1] MD PhD

Affiliations: [1]Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [2]Department of Hematology and Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Corresponding Author: Neda Nikbakht MD PhD, Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, 233 South 10th Street, Room 410, Philadelphia, PA 19107, Tel: 215-503-4834, Fax: 215-503-5788, Email: neda.nikbakht@jefferson.edu

Abstract

A 68-year-old woman with a history of seizures on cenobamate presented with an itchy rash all over her body. The rash started about one month prior to her presentation to the dermatology clinic. The rash was initially treated with topical triamcinolone with improvement at one-month follow-up. However, four months later the rash flared and there was concern that cenobamate was the cause. Biopsy was performed showing vacuolar interface dermatitis with atrophy, suggestive of subacute lupus erythematosus. Blood work revealed positive antinuclear antibody, anti-ribonucleoprotein antibody, Sjogren Anti-SS-A and positive histone antibody. Given the worsening rash, positive labs, and cenobamate as the only changed drug several months before initial onset, she was diagnosed with drug-induced subacute cutaneous lupus erythematous and her cenobamate was discontinued. To the best of your knowledge, this is the first reported case of a medication in the carbamate family leading to drug induced subacute cutaneous lupus erythematosus.

Keywords: cenobamate, drug reaction, lupus

Introduction

The first description of drug-induced subacute cutaneous lupus erythematous (DI-SCLE) dates to 1985 when a series of five patients were found to have hydrochlorothiazide-induced subacute cutaneous lupus erythematous [1]. An increasing number of drugs have been known to cause DI-SCLE [2]. The number of novel medications approved by the Center for Drug Evaluation and Research in the United States has been steadily increasing since 2008 [3]. As new medications continue to be approved, the possibility of unforeseen DI-SCLE rashes arises. We present a woman with a history of uncontrolled seizures who was started on a recent FDA approved antiepileptic drug, cenobamate, who then presented with a rash and was diagnosed with DI-SCLE.

Case Synopsis

A 68-year-old woman with a history of epilepsy presented with a mildly itchy rash for a duration of one month. Eight months prior due to uncontrolled seizures her neurologist had switched her antiepileptic medication from pregabalin to cenobamate. She was started on 12.5mg of cenobamate daily with instructions to increase to 200mg over the course of 12 weeks.

On physical examination, she had erythematous-to-dusky plaques on the arms, legs, and trunk (**Figure 1**). She was prescribed topical triamcinolone twice daily with some improvement initially. She returned four months later with a worsening rash consisting of erythematous plaques on the back, arms, and legs with overlying scale despite triamcinolone ointment twice daily.

A biopsy was performed which revealed acute vacuolar interface dermatitis with the atrophy of the epidermis favoring an acute expression of autoimmune connective tissue disease such as subacute cutaneous lupus erythematous (SCLE),

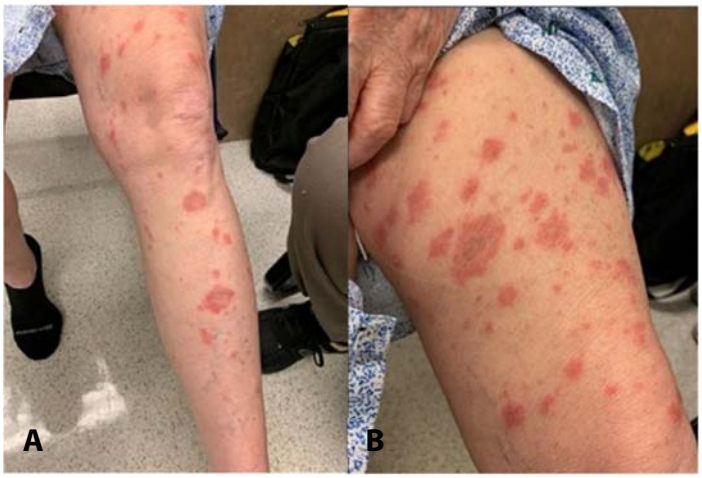

Figure 1. ***A)*** *Erythematous to dusky plaques on the left lower leg.* ***B)*** *Erythematous to dusky plaques on the left upper thigh.*

(**Figure 2**). Autoimmune blood workup revealed a positive antinuclear antibody of 1:320, positive anti-ribonucleoprotein antibody at 2.3AI (reference range 0.0-0.9AI), positive histone antibody at 1.6 Units (reference range: negative <1.0 Units), Sjogren anti-SS-A of greater than 8.0AI (reference rage; 0.0-0.9AI), low complement C4 at <2mg/dl (reference range 12-38mg/dl), and negative anti-dsDNA antibody.

In the absence of any history of autoimmune disease, signs or symptoms of systemic disease and with the introduction of cenobamate, a diagnosis of cenobamate DI-SCLE was made. As a result, cenobamate was discontinued and the patient was placed on another epileptic drug. Her rash significantly improved within two weeks after stopping cenobamate with only residual rash on the legs and back. Two weeks later because the residual rash was not resolved she was started on hydroxychloroquine which resulted in complete resolution of her rash after two months of therapy. At follow-up six months later she continued to be rash free. However, she subsequently developed leukopenia, mildly elevated creatinine, and her C4 complement levels continued to be low. This indicated that she continued to have ongoing lupus activity despite cessation of the offending drug. As such, she continues to remain on hydroxychloroquine and will be monitored for disease activity over time.

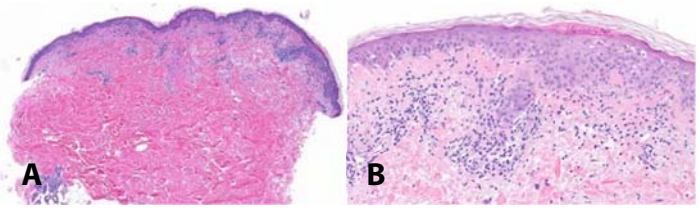

Figure 2. *H&E histopathology.* ***A)*** *Punch biopsy of a lesion from the back reveals acute vacuolar interface dermatitis with the atrophy of the epidermis, 20×.* ***B)*** *Patchy lymphocytic infiltrate in the superficial dermis with extension into the epidermis. There is notable epidermotropism of lymphocytes in the epidermis with minimal corresponding spongiosis. There appears to be scattered areas of vacuolization at the basement membrane layer. Epidermal layer appears diffusely atrophied while maintaining normal keratinization, 400×.*

Case Discussion

Drug-induced subacute cutaneous lupus erythematous is a type of SCLE in which the disease onset is associated with the ingestion of an offending medication [2]. It is estimated that approximately one-third of all SCLE cases are drug-induced [2]. It can often be difficult to distinguish idiopathic SCLE and DI-SCLE as they are serologically, histopathologically, and clinically the same [4]. Antihypertensives including thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers have been known to cause DI-SCLE. Other classes of drugs strongly linked to causing DI-SCLE include proton pump inhibitors, nonsteroidal anti-inflammatory drugs, chemotherapeutics, terbinafine, simvastatin, interferon alfa and beta, leflunomide, and carbamazepine [4].

The pathogenesis of SCLE is multifactorial and is believed to develop owing to genetics, environmental triggers, or immunologic factors. Several factors play a role in the development of SCLE which include genes such as HLA1, C4 null ancestral haplotype, deficiencies of C2 and C4 components of complement, and environmental factors such as UV light and drugs [5]. A person with these predisposing factors may have a low-grade susceptibility to SCLE that may be unmasked with drug triggers in patients with DI-SCLE.

Although the exact mechanism causing DI-SCLE is unclear, it has been suggested that certain

medications can trigger a photosensitive state that might induce SCLE lesions [6]. This hypothesis is supported by the fact that several medications known to trigger DI-SCLE such as hydrochlorothiazide, terbinafine, and etanercept are known to induce photosensitivity [6]. There have been cases of patients with pre-existing systemic lupus erythematosus who may have a higher predisposition to photosensitivity and thus may be especially susceptible to DI-SCLE [6]. Lastly, there are cases of patients with previous diagnoses of idiopathic SCLE in remission being exacerbated by proton pump inhibitors and patients with autoimmune connective tissue diseases developing DI-SCLE after use of proton pump inhibitor [7,8]. For our patient her low C4 complement level could have been a predisposing genetic factor for triggering DI-SCLE.

The timeline of DI-SCLE symptoms can range from weeks to many months after exposure to the triggering medication, making identification of the offending medication and diagnosis difficult [9]. Although there are no formal or standard diagnostic criteria for DI-SCLE, a high index of suspicion is needed for the diagnosis. Idiopathic SCLE and DI-SCLE are essentially identical in presentation and are both characterized by widespread erythematous annular-polycyclic or papulosquamous psoriasiform lesions [10,11]. However, in DI-SCLE the legs are more likely to be affected which are usually spared in idiopathic SCLE [12]. Widespread distribution of the rash and resolution of rash after discontinuation of the drug is consistent with DI-SCLE rather than idiopathic SCLE [13]. Also, most patients affected by DI-SCLE are older females [72%] with a mean age of 58.0 years as opposed to idiopathic SCLE affecting younger females [14]. Antinuclear antibody and anti-Ro/SS-A are just as prevalent in drug-induced and idiopathic SCLE with antihistones present in up to 33% of patients with DI-SCLE [14].

The primary treatment of DI-SCLE is identification and removal of the offending medication. Most cases of DI-SCLE resolve in weeks to months following the cessation of the offending drug. Some cases do not resolve spontaneously and require additional treatment as was observed in our case with the addition of hydroxychloroquine [6]. There are also other documented cases requiring active treatment for DI-SCLE resolution [10]. Lastly, according to Lowe et al., the overwhelming majority of patients who experienced DI-SCLE have not been reported to progress to idiopathic systemic lupus erythematosus or Sjögren syndrome. However, this may relate to the follow-up intervals been relatively short. Farhi *et al.* reported a man on terbinafine who, four months after remission from DI-SCLE, presented with signs and symptoms of systemic lupus erythematosus. The patient presented with a malar rash, acute thrombocytopenia, leucopenia, neutropenia and lymphopenia [15]. Goodrich and Kohn reported an antinuclear antibody+ woman on hydrochlorothiazide who presented 6 months after DI-SCLE resolution with pneumonitis that was presumed to be lupus pneumonitis [16].

When compared to an original systematic review of DI-SCLE in 2009 by Lowe et al. [10], a new study showed a relative change in drug classes causing DI-SCLE from 2009 to present [4]. The greatest shift in drug class reporting was seen with proton pump inhibitor medications increasing by 34.1%. For less common drug classes such as antiepileptics, cases decreased by 0.5% [10]. Antiepileptics including carbamazepine and phenytoin represented 2.6 % of the original reported cases of DI-SCLE [1].

Cenobamate, the most recent drug of the series of alkyl-carbamates developed and approved by the FDA in 2019 for epilepsy therapy, showed remarkable antiseizure efficacy in clinical trials. This drug brings substantial promise for patients with focal seizures that have been difficult to control with other medications along with the potential for freedom from seizures [17]. The only reported rash from the antiepileptic drug cenobamate is related to drug reaction with eosinophilia and systemic symptoms [17,18]. Studies have also shown that rapid titration of cenobamate can cause hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms [17,18].

Conclusion

We present a patient diagnosed with DI-SCLE triggered by cenobamate. There are many drugs which have been implicated in DI-SCLE. Although antiepileptics are very uncommon in causing DI-

SCLE, physicians should have a high index of suspicion for DI-SCLE in patients presenting with a new rash who have been prescribed such medications. There should be a detailed and extended medication history with a trial cessation of the drug in these patients. A very thorough extended drug history going back almost one year and improvement of the rash following the cessation of the suspected drug can confirm the diagnosis of DI-SCLE. It may also be reasonable to consider DI-SCLE evaluation in any case of newly-diagnosed SCLE. Physicians should keep in mind that when prescribing cenobamate, as is the case for several other antiseizure drugs, safety concerns with cenobamate can be at least partly mitigated by cautious titration. Lastly, we recommend that perhaps patients should be monitored for a longer period after cessation of the offending agent as residual disease activity for lupus may persist well beyond drug cessation. Further studies and clinical experience are needed to investigate the association of cenobamate and DI-SCLE. Further studies are also needed to investigate the mechanism of predisposition and susceptibility to DI-SCLE especially in patients without a previous diagnosis of SLE.

Potential conflicts of interest

The authors declare no conflicts of interest.

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