

Lamotrigine Subacute Cutaneous Lupus Erythematosus

Pizzatti L¹, Rongioletti F¹, Pilloni L², and Atzori L^{1*}

¹Dermatology, Department Medical Sciences and Public Health, University of Cagliari, Via Ospedale 54, 09124 Cagliari, Italy

²Pathology Service- Department Medical Sciences and Public Health, University of Cagliari, Via Ospedale 54, 09124 Cagliari, Italy

*Corresponding author: Atzori Laura, Clinica Dermatologica, Via Ospedale 54- 09124 Cagliari, Italy, Tel: + 00390706092324; Fax: 00390706092580; E-mail: atzoril@unica.it

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Abstract

Objective: Lamotrigine is a new generation anticonvulsant, also used in bipolar type 1 disorders to prevent occurrence of mood episodes not responding to traditional antidepressants, which is an increasing indication worldwide. Skin adverse events occur in 5-10% of patients, but are usually mild and self-limiting. The occurrence of drug-induced lupus erythematosus is an uncommon, but severe condition, usually requiring discontinuation of the drug.

Methods: A spontaneous pharmacovigilance case reporting is presented, following the causality assessment criteria, including temporal association with drug exposure, exclusion of other etiologies, dechallenge and rechallenge. Skin biopsy for normal histopathology and direct immunofluorescence was performed to assess the diagnosis of lupus erythematosus.

Results: A 77 years old woman was hospitalized in the Dermatology Clinic of Cagliari University for a lamotrigine Induced Subacute Cutaneous Lupus Erythematosus, confirmed by improvement after drug discontinuation, and immediate recurrence at re-exposure. The last measure was performed on request of the neurologist with the consent of the patient, because of a high suicidal risk, not responding to traditional antidepressants, and well controlled by lamotrigine. Another peculiarity of our observation is a potential dose-related effects, as the patient was assuming lamotrigine from 2 years, and skin manifestations actually began 3 weeks after the dosage was doubled to 100 mg daily.

Conclusion: If confirmed by other observations, drug-induced subacute cutaneous lupus erythematosus might be dose-dependent, and careful clinician's dosage monitoring might prevent occurrence, preserving the lamotrigine use for the many patients who need it. Dermatologist referral is warranted in front of any suspected cutaneous adverse reaction due to psychotropic medications, to provide prompt recognition, adequate assessment and supportive management of such difficult and delicate patients.

Keywords: Lamotrigine; Drug-induced Subacute lupus erythematosus; Drug causality assessment; Adverse drug reaction

Abbreviations: DILE: Drug Induced Lupus Erythematosus; DI-SCLE: drug-induced Subacute Cutaneous Lupus Erythematosus; SCLE: Subacute Cutaneous Lupus Erythematosus; HLA: human leukocyte antigen; DRESS: Drug Reaction with Eosinophilia and Systemic Symptom Syndrome; DIHS: Drug Induced Hypersensitivity syndrome; TEN: Toxic Epidermal Necrolysis; ANA: Antinuclear Antibodies

Introduction

Various drugs may induce an autoimmune response, which can lead to the production of auto antibodies. Some patients (about 10-15% of cases, 15,000 to 30,000 cases in the United States) [1]. May develop Drug Induced Lupus Erythematosus (DILE), a lupus-like condition related to chronic drug exposure, which usually resolves after discontinuation of the drug. In the spectrum of DILE manifestations, skin involvement is a predominant feature, the drug-induced Subacute Cutaneous Lupus Erythematosus (DI-SCLE) representing 70-80% of cases [2,3]. A case-control study that valued

234 patients with SCLE found out that more than 1/3 of those cases was related to drug exposure [4]. Another retrospective study showed that among 448 cases of CLE, 10% was drug-induced [5]. Moreover, drugs may potentially cause the exacerbation of pre-existing lupus in predisposed patients. The mechanism involved in the pathogenesis of DILE remains uncertain, however possible genetic risk factors include human leukocyte antigen HLA-DR4, HLA-DR0301, and the complement C4 null allele [6,7]. Regardless of the mechanism, the pathogenesis results in an enhanced

autoimmunity and the clinical manifestations reflects the immune-mediated effects on the target organs, leading to a variety of systemic signs and symptoms. The list of medicaments associated with DILE is increasing every year, including hydralazine, procainamide, quinidine, isoniazid, minocycline, diltiazem, statins and TNF inhibitors, for systemic lupus, while DISCLE, is mostly caused by chemotherapeutic agents, hydrochlorothiazide, antihypertensive agents, terbinafine, and recently proton pump inhibitors [8]. Lamotrigine is a new generation anticonvulsant drug used widely to treat epilepsy, but with an increasing indication in the maintenance treatment of bipolar type I disorders to prevent occurrence of mood episodes

(depression, mania, hypomania) [9]. The drug is a voltage-dependent sodium channel inhibitor which produces a block of prolonged repetitive neuronal discharges and inhibits the release of glutamate. It has various neurologic, gastrointestinal and cutaneous adverse reactions. It has been estimated that between 5 and 10% of patients treated with lamotrigine present a benign cutaneous reaction, whereas around 0,3% could develop a severe skin rash with systemic involvement [10,11]. The occurrence of DILE has been rarely reported, with only 5 cases described so far (Table 1). We present a further case of Lamotrigine-induced SCLE, with a comparison to previous reports.

Table 1: Lamotrigine drug-induced lupus case collection from the literature.

Reference	Age	Gender	Clinical Manifestations	Laboratory	Latency	Dechallenge	Rechallenge
Sarzi-Puttini et al. 2000	57	Female	Malar Rash, Photosensitivity	ANA positivity	3 years	Yes	No
Ravindran et al. 2011	18	Female	Facial Rash, Oral Ulcers, Arthralgia	ANA positivity	18 months	Yes	No
Cabanillas et al. 2012	48	Female	Annular Plaques on Trunk and Arms	ANA, anti-histone positivity	4 years	Yes	No
Chang et al. 2014	39	Female	Recurrent Arthralgia	ANA positivity	Not reported	Yes	No
Batra et al. 2018	22	Female	Photosensitivity, Oral Ulcers, Rash on Face, Trunk And Upper Limbs	ANA, anti SSA/Ro, SS-B/La positivity	2 months	Yes	no

Case Presentation

A 77 years old woman presented in October 2016 with a 5-month history of very itching, erythematous edematous manifestation on photo-exposed areas of the face, hands, and upper trunk. She was under medical treatment from 2015 with Lamotrigine 50 mg/die for a major recurrent depression with suicidal tendencies. In addition, she has been taking Sertraline, Clonazepam, Pravastatin and Propranolol from several years, without skin adverse events. Three weeks before skin manifestation onset, for an involuntary pharmacist error, the patient was assuming a double dose of lamotrigine (100 mg daily). The over-dosage was recognized after the careful dermatologist investigations on drug history, and was immediately take over by the neurologist, slowly tapering the dosage until dismissal. Clinical examination revealed symmetrical erythematous and scaly plaques, sometimes with

adherent scales, especially on the face and ears, but with a crusting exudative surface on chest, upper back, and limbs, especially the dorsal side of hands (Figure 1, left boxes). In the suspect of a vesical-bullous reaction, a skin biopsy was performed for standard hematoxylin-eosin staining, and direct immunofluorescence. Surprisingly, the microscopic features showed a prevailing interface dermatitis, with perivascular superficial and interstitial dermatitis, mixed cell exudate, associated with focal dermo-epidermal fissures including frequent neutrophil granulocytes with scattered apoptotic bodies and vacuolar degeneration of basal keratinocytes (Figure 2, inset a, b). Direct immunofluorescence showed linear positivity at the dermo-epidermal interface, intense for C3c (Figure 2, inset c), mild for IgG; IgA and IgM were negative.

Figure 1: Lamotrigine subacute cutaneous lupus, presenting with symmetrical erythematous and scaly plaques, with a crusting exudative surface on upper back, dorsal side of hands (left boxes); rapidly improvement after drug discontinuation (central boxes), and worsening after reintroduction (right boxes).

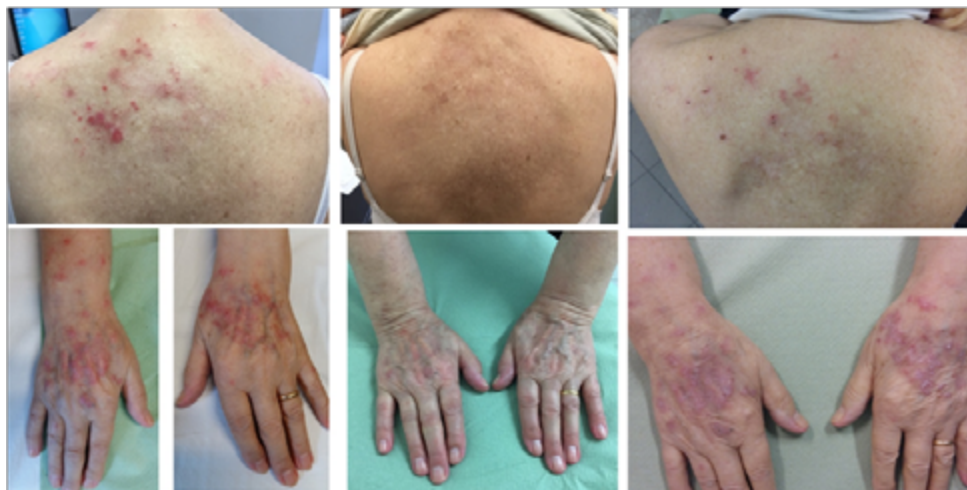
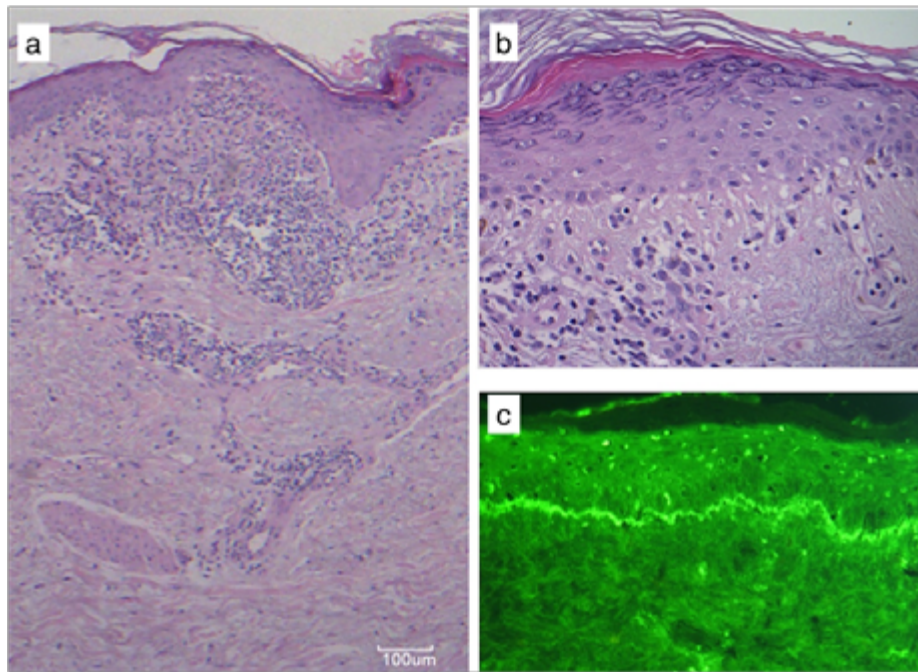


Figure 2: Skin biopsy histopathological findings: prevailing interface dermatitis, with perivascular superficial and interstitial inflammatory infiltrate, mixed cell exudate (inset a: Hematoxylin and Eosin stain, magnification 4x), associated with frequent neutrophil granulocytes with scattered apoptotic bodies and vacuolar degeneration of basal keratinocytes (inset b: H&E 10x). Direct immunofluorescence showed linear positivity at the dermo-epidermal interface for C3c (inset c, 10x).



Laboratory investigations showed a hypochromic anemia, elevated erythrocyte sedimentation rate (ESR: 33 mm) and C-reactive protein (21, 3 mg/dl). Serum Antinuclear Antibodies (ANA) were negative, while anti SSA/Ro, anti dsDNA and anti-histones were positive (respectively 23 U/ml, 55 U/ml, 36,1 U/ml). Urine analysis, ECG and chest X-Ray were normal. We also made an ophthalmological counseling which showed a hereditary maculopathy. Given the strong temporal relationship between Lamotrigine assumption, especially with the recent accidental over-dosage and clinical manifestation, the positivity of auto-antibodies and the histological examination, a diagnosis of SCLE triggered by Lamotrigine was made. Itching and skin lesions had rapidly improved with drug dismissal (Figure 1, central boxes), and the decision not to introduce corticosteroid oral treatment was taken, also considering the suicidal risk. Hydroxychloroquine administration was excluded because of the ocular hereditary maculopathy. In the following months, prescribing simple mixed corticosteroid and antibiotic creams, plus strict photoprotective creams and physical measures, a complete resolution of the clinical manifestations was observed, together with a slow decrease of serum auto-antibodies. In contrast, her neuropsychiatric status was gradually worsening, with recurrence of crisis and aggravation of suicidal tendencies. According with her neurologist and after written consent from the patient and her relatives, we therefore decided to re-introduce Lamotrigine, at the minimal dosage of 25 mg/daily. After 2 weeks, the skin manifestations relapsed on the same initial site of involvement (Figure 1, right boxes), and the decision to definitely withdraw lamotrigine was taken. The patient has been visited regularly every 3 months for the following year without new lesions, including the summer period which could have represented a natural trigger for relapse. Autoimmunity remained altered: anti SSA/Ro, anti dsDNA remained positive at low title. Only anti-histones were negative at the 9 month-follow-up. (Figure 1, Figure 2).

Discussion

Chronic exposure to various medicaments may induce lupus erythematosus occurrence, and lamotrigine has been recently included in the list of rare, anecdotal observations [12-16]. The presented case is the first to confirm a certain association, respecting all criteria usually applied for drug causality assessment, such as the Naranjo algorithm [17]. Manifestations were initially atypical, more eczematous and suggesting a vesical-bullous eruption, which immediately alerted on the possibility of a severe adverse reaction, in the spectrum of Stevens-Johnson and toxic epidermal necrolysis, which have been widely associated to lamotrigine exposure [18]. However, DISCLE often presents with polymorphous annular or papulosquamous plaques that involve sun-exposed skin, and bullous and erythema multiforme-like lesions are described [19,20]. It rarely exhibits general or visceral manifestations, in contrast with its idiopathic counterpart, where the prevalent features include systemic symptoms, particularly arthralgia, xerophthalmia and nephropathy [21]. Concerning laboratory test, our case differs from lamotrigine DILE Literature in serological expression, because of the absence of ANA antibodies, although SSA/Ro, SSB/La and anti-histones resulted positive. Besides, the ANA negativity is reported in about 20% of DISCLE patients, and it is actually recommended to perform ENA testing, especially for anti SSB/La positivity and anti-histone when the clinical history is evocative of lupus cutaneous. The anti-histone antibodies are otherwise not often positive in DISCLE, being more often associated with systemic DILE [22]. This finding prompts us to be more cautious towards a possible evolution of the reaction into DILE. Persistence of the positive autoimmunity is a plausible explanation of the individual predisposition to Lupus Erythematosus, and might be an indication to serological screening of patients before lamotrigine exposure.

Moreover, our patient was the oldest among all cases (77 years), fact which is in line with the general observation that DILE occurs in patients older than 50 years [19,20]. The latency of clinical manifestations after drug introduction, according to DILE criteria, ranges from 3 days to 11 years [3-5,23]. In our case latency was of 21 months, although skin manifestations actually began when the lamotrigine dosage was doubled, although involuntary. If confirmed by other observation, drug-induced skin manifestations might be dose-dependent, and careful clinician's dosage monitoring might prevent occurrence, preserving the lamotrigine use for many patients with epilepsy or severe instable mood's disorders. A check for interaction (Drug Interaction Checker, Medscape and Drug Interaction report, Drugs.com) between lamotrigine and the other medications taken by the patients, (Sertraline, Clonazepam, Pravastatin and Propranolol) did not retrieved particular warning for skin toxicity. All those medications were regularly assumed for more than 5 years without any adverse skin reaction, which was instead noted after lamotrigine introduction. Nevertheless, the chances of the ADR occurring due to the combination of drugs rather than lamotrigine alone cannot be excluded and is worth consideration.

Conclusion

Lamotrigine is a very rare cause of DILE, and so far, only anecdotal reports were available. The drug causality assessment following Naranjo pharmacovigilance algorithm in our case is certain, having the opportunity to observe the response to lamotrigine de-challenge and re-challenge. Clinical, immunological and histopathological features classified the reaction as a form of SCLE, representing the second reported case of lamotrigine DISCLE. Although skin manifestations were mild and controlled with topical treatment, the immunological profile, with high anti-histone title, and the previous reports of DILE suggested the risk of a potential evolution into a systemic form. Strict neurologist and dermatologist cooperation were necessary to manage this very complex case, at high suicidal risk, which highlight the need to careful consider the risk of cutaneous adverse reactions due to psychotropic medications.

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