

Carbamazepine-induced systemic lupus erythematosus: A case-based review

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Abstract

A case of carbamazepine-induced systemic lupus erythematosus (CBZ-DILE) is presented, along with a literature review, with the aim to define the clinical and serological characteristics of this group, and compare them with systemic lupus erythematosus (SLE) triggered by other drugs (DILE). A 31-year-old woman presented with a 6-month history of hand arthritis and nasal ulcers. She had been diagnosed with epilepsy at 12 years of age and had continued treatment with carbamazepine (CBZ) for the past 18 years with excellent clinical control. Laboratory data revealed antinuclear antibodies (ANA) positive to a titer of 1/1280, and positive anti-nucleosome antibodies. The patients' clinical symptoms disappeared after the CBZ discontinuation and did not reappear during the 1-year follow-up period. A search was made in the PubMed/Medline database of the (CBZ-DILE) published cases. A total of 26 cases of CBZ-DILE were found in the search. CBZ-DILE cases are characterized by variable latency periods that often last for years and are not related to the dose of CBZ. Most frequent clinical findings of CBZ-DILE in patients are arthralgia/arthritis, mucocutaneous manifestations, constitutional symptoms, and pleuritis or pericarditis. The renal involvement has not been reported in CBZ-DILE. Antihistone antibodies were observed less frequently, and anti-dsDNA antibodies were observed more frequently than in the "classic" DILE. The ANA remained positive in over 60% of cases during the follow-up after withdrawal. The CBZ-DILE has significant clinical and laboratory manifestations that distinguish it from classic DILE or idiopathic SLE.

Keywords: Anticonvulsant drugs, antiepileptic drugs, carbamazepine, drug-induced systemic lupus erythematosus, systemic lupus erythematosus

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Introduction

Various drugs can trigger the appearance of symptoms and laboratory findings similar to systemic lupus erythematosus (SLE), with this clinical picture being known as drug-induced lupus erythematosus (DILE). It is thought that the frequency of DILE may be underestimated, since many of the cases are mild, and probably only a small percentage is correctly diagnosed, with it being estimated that DILE represents 10% of all SLE cases (1). A large number of drugs from different therapeutic families have been described as triggers of DILE, including antiarrhythmic, antihypertensive, antipsychotic, antibiotic, anticonvulsant, antithyroid, anti-inflammatory, diuretic, cholesterol-lowering (statins), and biological drugs, as well as miscellaneous others (2). Many of these drugs often induce antibody production, but they do not produce signs or symptoms of associated disease (2, 3).

Various antiepileptics have been implicated as causing factors of DILE, including phenytoin, trimethadione, primidone, ethosuximide, clobazam, valproic acid, and carbamazepine (CBZ) (1, 4). CBZ, is a drug commonly used for the treatment of epilepsy, psychiatric illnesses (bipolar disorder, major resistant depression, and borderline states), and chronic pain syndromes (5). Although CBZ is usually well tolerated, the potential adverse effects of the therapy may vary from mild symptoms to severe systemic reactions. Common adverse effects include drowsiness, diplopia, and cerebellum dysfunction, which are dose dependent, as well as idiosyncratic leukopenia. Various hypersensitivity reactions have also been described in relation with CBZ, including erythema multiforme, Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), pseudo-lymphoma, aplastic anemia, agranulocytosis, and pancreatitis, as well as several autoimmune disorders, including vasculitis, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, and DILE (5, 6).

Since the initial description by Simpson in 1966 (7), several cases of carbamazepine-induced systemic lupus erythematosus (CBZ-DILE) have appeared in the medical literature. A new case of CBZ-DILE is described, along with a literature review, adding the cases published in the last years, with the aim of defining the clinical and serological characteristics of this group, and comparing them with those SLE triggered by other drugs.

Case Presentation

A 31-year-old woman was seen in the Rheumatology Clinic due to a history of 6-month onset of pain and swelling in the hands. Furthermore, in the last year, she presented with frequent nasal ulcers. She had no fever or deterioration in her general health status. Diagnosed with epilepsy at the age of 12, with partial seizures, she has been on CBZ treatment (300 mg twice daily) for 18 years, with good clinical control.

Fifteen years ago, an attempt was made to withdraw the antiepileptic medication, but with the appearance of new seizures, it was decided to maintain the treatment. The cardiac-pulmonary auscultation was normal in the physical examination, with arthritis being observed in the carpal, metacarpophalangeal, and proximal interphalangeal joints. No skin lesions, enlarged organs, or swollen lymph glands were observed. The complete blood

Table 1. Papers and patient's characteristics

Author (year)	Age/Sex	Clinical Features	ANA	Anti-dsDNA	Anti-histone	Results of stopping CBZ
1. Simpson (1966) (7)	63/F	Rash, malaise, axial pain	NA	NA	NA	Recovery. ANA: NA
2. Livingston (1967) (11)	46/F	Arthritis, rash, fever	NA	NA	NA	Recovery. ANA: NA
3. Beurey (1972) (12)	42/F	Arthralgia, rash, fever	+	NA	NA	Uncertain. ANA: NA
4. Takigawa (1976) (13)	25/F	Arthritis, rash, oral ulcers	+	NA	NA	Recovery. ANA: NA
5. Kolstee (1983) (14)	25/M	Arthritis	+	NA	NA	Recovery. ANA: NA
6. Bateman (1985) (15)	30/F	Arthralgia, rash, pleuritis	+	+	NA	Recovery. ANA+
7. McNicholl (1985) (16)	14/F	Arthritis, rash	+	+	NA	Recovery. ANA+
8. Alballa (1987) (8)	23/F	Arthritis, rash	+	-	+	Recovery. ANA-
9. Drory (1989) (17)	18/M	Arthralgia, rash, fever, pleuritis, pericarditis	+	+	NA	Recovery. ANA+
10. Öner (1990) (18)	16/F	Arthritis, rash	+	+	NA	Uncertain. ANA+
11. De Giorgio (1991) (19)	20/F	Fever, malaise	+	-	NA	Recovery. ANA-
12. Kanno (1992) (10)	14/F	Rash, fever, adenopathies	+	-	-	Recovery. ANA+
13. Schmidt (1992) (20)	21/F	Arthritis	+	+	+	Uncertain. ANA+
14. Boon (1992) (21)	22/M	Arthritis	+	-	+	Recovery. ANA+
15. Ohashi (1993) (22)	39/F	Miositis	+	NA	NA	Recovery. ANA: NA
16. Ghorayeb (1996) (23)	23/F	Arthritis	+	+	-	Recovery. ANA-
17. Reiffers (1997) (24)	40/F	Rash, Raynaud	+	+	+	Recovery. ANA+
18. Milesi-Lecat (1997) (25)	52/F	Arthralgia, rash, hair loss, bronchiolitis obliterans	+	-	+	Recovery. ANA+
19. Toepfer (1998) (26)	34/M	Arthritis, rash, photosensitivity, pleuritis	+	+	+	Recovery. ANA-
20. Bachmeyer (1998) (27)	27/M	Arthralgia, fever	+	+	+	Recovery. ANA+
21. Verma (2000) (5)	45/M	Pericarditis, pleuritis	+	-	+	Recovery. ANA: NA
22. Motta (2006) (28)	30/F	Arthritis	+	-	-	Recovery. ANA+
23. Wittchen (2006) (29)	35/M	Rash, pericarditis, pleuritis, adenopathies	+	+	+	Recovery. ANA-
24. Pelizza (2006) (6)	38/F	Arthritis, rash, photosensitivity, fever, adenopathies, miositis	+	-	+	Recovery. ANA-
25. Molina-Ruiz (2017) (30)	9/F	Arthralgia, rash, oral ulcers, fever, malaise, adenopathies	+	-	+	Recovery. ANA-
26. Haydari (2017) (31)	34/F	Pericarditis	+	-	+	Recovery. ANA: NA
27. Present case	31/F	Arthritis, nasal ulcers	+	-	-	Recovery. ANA+

F: female; M: male; ANA: antinuclear antibodies; Anti-dsDNA: antibody to double-stranded DNA; +: positive; -: negative; NA: not available; CBZ: carbamazepine; Recovery: clinical recovery; Uncertain: uncertain clinical recovery; ANA:NA: ANA not available at follow-up time; ANA+: ANA persistence at follow-up time; ANA-: ANA negativization at follow-up time

count results showed a hemoglobin of 11.5 g/dL, with a hematocrit of 32.5%. The white cells were normal, as well as their differential count and number of platelets. The liver and kidney function tests were normal, as well as the thyroid hormones and the hepatitis B and C serology. The rheumatoid factor was negative, and the antinuclear antibodies (ANA) were positive to a titer of 1/1280 (homogeneous pattern), and positive anti-nucleosome antibodies. The rest of the antibodies were negative, including anti-dsDNA, anti-histones, anti-Sm, anti-RNP, anti-Scl70, anti-PMScl, anti-Ro/SSA, anti-La/SSB, anti-Jo1, anti-centromere, anti-PCNA, anti-ribosomal P, anti-neutrophil cytoplasmic antibodies (ANCA), and anticardiolipin IgM/IgGs. The complement levels were low, with a C3 of 62 mg/dL (normal: 90-180) and a C4 of 6 mg/dL (normal: 10-40).

The patient was diagnosed with probable lupus induced by CBZ, and treatment with hydroxychloroquine (200 mg/day) was started. The Neurology Department was consulted on the withdrawal or change of anticonvulsant treatment. An EEG was performed, in which the presence of irritative activity was observed in the left anterior temporal region, for which treatment was initiated with levetiracetam (1000 mg twice daily), with the gradual withdrawal of CBZ. The clinical symptoms of the patient disappeared after the CBZ withdrawal. The hydroxychloroquine was discontinued as well, and the lupus clinical symptoms did

not reappear during the 1-year follow-up. The ANA remained positive to a lower titer (1/640) during that same period, with negativization of anti-nucleosome antibodies.

Literature Review

In addition to the case presented, reports of CBZ-DILE were identified using the PubMed/Medline database. The following combined two groups of keywords were used: (lupus, systemic lupus erythematosus, SLE, lupus-like, SLE-like, drug induced lupus) and (carbamazepine, Tegretol, anticonvulsant). Reports of CBZ-DILE from databases were included if clinical information was available. The search was conducted in February 2018.

Three series (8, 9, 10), with a majority of coincident cases and several isolated cases (5, 6, 7, 9, 10-31) of CBZ-DILE, have been published with clinical information on patients taking CBZ, up to a total of 27 cases, including our patient (Table 1). Two cases of CBZ-induced cutaneous lupus were also found (32, 33), as well as 2 cases of DILE in patients taking the drug analogue oxcarbazepine (34, 35).

Of the 27 CBZ-DILE cases described, 20 occurred in women and 7 in men. The mean age when the DILE symptoms appeared was 30.2 years±12.4 (range 9-63), with 26 of the 27 cases younger than 50 years. The mean time between the start of treatment with CBZ and the appearance of the clinical picture of DILE

was 36.5±60.2 months (range 1-240), being greater than 1 year in 12 of the cases. The CBZ dose used was 200 mg/day in 2 cases, 400-800 mg/day in 17 cases, and 1000-1600 mg/day in 4 cases, with no data being available on the other 4 patients. The symptoms that led to the use of CBZ were epilepsy in 22 cases, psychiatric alterations in 4 cases, and facial pain in 1 case. The most frequent signs of DILE were arthralgia/arthritis in 19/27 (70.4%), rash in 16/27 (59.2%), fever/malaise in 8/27 (29.6%), pleuritis/pericarditis in 6/27 (22.2%), swollen lymph nodes in 4/27 (14.8%), oral or nasal ulcers in 3/27 (11.1%), photosensitivity in 2/27 (7.4%), myositis in 2/27 (7.4%), and alopecia, Raynaud, splenomegaly, and obliterative bronchiolitis in 1 case each. No renal or neurological changes associated with lupus were observed.

Considering the changes in the laboratory tests, hematological anomalies (anemia, leucopenia, lymphopenia, thrombopenia) were mentioned in 12 (44.4%) cases. ANA were positive in all cases, except in the first 2 cases described, as there were no data available. Anti-dsDNA were positive in 10 out the 21 cases (47.6%) in which this determination was performed, as well as the anti-histone antibodies in 12 of the 16 cases (75%) in which they were analyzed. LE cells were positive in 4 cases, anti-Sm/RNP antibodies in 2 cases, and anti-SSA, anti-nucleosomes, and anticardiolipin, in 1 case each. A low complement was observed in 6 cases. The HLA profile was reported in 6

Table 2. Differences between idiopathic SLE, "classic" DILE, anti-TNF-α DILE and CBZ-DILE

	Idiopathic SLE *	"Classic" DILE *	Anti-TNFα DILE **	CBZ-DILE
Clinical features				
Gender predisposition (F / M)	9 / 1	1 / 1	5/1	3 / 1
Arthralgias/arthritis	++++	++++	+++	+++
Rash (all)	+++	++	+++	+++
Fever/malaise	++++	+++	+++	++
Pleuritis/pericarditis	+++	++	++	++
Renal involvement	+++	+	+	-
Neurologic involvement	+++	+	+	NA
Laboratory features				
Hematologic	++++	+	+++	+++
ANA	++++	++++	++++	++++
Anti-dsDNA	++++	+	++++	+++
Anti-histone	+++	++++	+++	+++
Low complement levels	+++	+	+++	++

Abbreviations: SLE: Systemic lupus erythematosus. DILE: Drug induced lupus erythematosus. CBZ: Carbamazepine. F: female. M: male. NA: Not applicable. ANA: antinuclear antibodies. Anti-dsDNA: antibody to double-stranded DNA. +++++: > 76%. +++: 41-75%. ++: 11-40%. +: 1-10%. -: 0%. "Classic" DILE refers to procainamide and hydralazine-induced DILE. * Data collected from references 2,3,46. ** Data collected from references 42,43,48.

patients. HLA-DR4 was present in 3 cases and the HLA-DR2, A1, A3, and B7 in 2 cases each. One patient had both HLA-DR2 and HLA-DR4.

In all cases, it was observed that all the clinical symptoms were resolved after the CBZ withdrawal, except in 3 cases (11, 18, 20) in which the outcomes were not completely clear. As well as the CBZ discontinuation, treatment with corticosteroids was required in 12 cases, with antimalarial drugs in 5 cases, and with immunosuppressants in 2 cases. The clinical resolution occurred between 1 week and 18 months after the CBZ withdrawal. The recurrence of symptoms was observed in 1 case after the reintroduction of CBZ, and in another case the ANA became positive, with no clinical reactivation, after reintroducing CBZ. Although there are also descriptions of DILE with oxcarbazepine (34, 35), in 1 case, the signs and symptoms were resolved after changing the CBZ for oxcarbazepine (21). In 1 patient, the appearance of lupus symptoms was mentioned in association with other anticonvulsants (10). In 7 of the 19 cases with data available, the ANA had returned to being negative between 3 and 30 months, whilst in the other 12 of the 19 (63.1%), the ANA remained positive during the variable time of the follow-up, although usually at lower titers and some specificities becoming negative. There were no deaths.

Discussion

The diagnosis of DILE is based on the presence of three criteria recognized by the majority of authors (10, 36): 1) the absence of lupus signs before starting the treatment that induced it; 2) the presence of at least one clinical sign of SLE, plus characteristic immunology anomalies; 3) disappearance of the clinical and biological signs with the treatment discontinuation. The clinical picture of DILE is generally milder than that of SLE (2, 3), and the resolving of the symptoms after withdrawing the inducing drug is fundamental in its interpretation as a DILE.

Many drugs are capable of inducing the appearance on ANA in a certain percentage of patients, but only a small number of patients develop a clinical picture of DILE (1, 3). The appearance of a positive ANA whilst receiving a drug susceptible to induce DILE signs, in the absence of clinical symptoms of lupus, is not sufficient for the diagnosis of a DILE, nor is it an indication for withdrawing the drug (1, 3). Several anticonvulsants are found among the drugs implicated as a cause of DILE, such as CBZ, phenytoin, ethosuximide, trimethadione,

primidone, valproic acid, and zonisamide. CBZ, like other antiepileptics, can induce the antibody production and DILE (37). In the work by Alarcón-Segovia in 1972, 170 epileptic patients were treated with different drugs, and 9 of them were treated with CBZ. More than three-quarters (78%) of this small subgroup had ANA to soluble nucleoprotein, and 11% anti-DNA antibodies, although with no other clinical or analytical evidence of SLE (37). However, in another study conducted on 58 children with epilepsy treated with CBZ alone, only 1 showed a positive ANA at a low titer (1/80) (38). This divergence of results could be due to the different sensitivities of the substrates used.

Among the antiepileptics, the risk of inducing a DILE appears higher with CBZ, although the risk is low (approximately 0.1% of patients treated during 1 year) (1). For other authors, the frequency of lupus-like symptoms induced by CBZ would be much less, being relegated to the isolated cases category, which is considered an incidence of <0.001% in treated patient (8) or 2-3 cases per 100,000 (19). Possibly, CBZ may not be such a rare inducer of SLE as it may seem in the medical literature. In a study based on the adverse effects data observed in primary care in the United Kingdom (UK General Practice Research Database), an increased risk of lupus was observed for CBZ (OR=1.88, 95% CI; 1.09-3.22), only surpassed by hydralazine and minocycline, although other drugs considered as high risk, such as procainamide, could not be evaluated due to the small number of treatments. The risk with CBZ was greater than that of quinidine, which is usually considered of moderate risk. On the other hand, the data indicated that this increase in risk was mainly restricted to women (39).

In the development of a lupus-like syndrome in a patient taking CBZ, three different scenarios may be considered (20): 1) A patient that suffers a neurological disease (e.g., epilepsy), and also an SLE-like syndrome induced by CBZ used for their treatment, which is resolved after its withdrawal, and would, strictly speaking, correspond to a CBZ-DILE. 2) A patient with subclinical SLE (the neurological signs may or may not be part of the SLE) that is triggered after the administration of CBZ. The CBZ, in this case, would act as a trigger of an idiopathic SLE, as can occur with exposure to sunlight, pregnancy, or estrogens (1). 3) A patient who suffers from a neurological disease treated with CBZ and who, independently of the treatment

with CBZ, develops an idiopathic SLE. Although Scenarios 2 and 3 are conceptually different, as in one CBZ acts as a trigger and not in the other, in clinical practice, it is difficult to separate them, and in both cases, the lupus will still be present or active despite the withdrawal of the CBZ or required follow-up with medication for the control of the SLE. These last two scenarios could correspond to cases in which recovery was not totally clear after the withdrawal of the CBZ or did not require follow-up with medication for the control of SLE (12, 18, 20). Our case would correspond to Scenario 1, where the clinical signs of lupus disappeared with the CBZ withdrawal, a situation that is not produced in Scenarios 2 and 3. A definitive causal relationship between CBZ and SLE is demonstrated in only 1 case, with the reappearance of the symptoms after the reintroduction of the CBZ (7). In the rest of the cases the causality is probable, based on the temporal relationship and principally on the clinical, and often analytical, recovery, after the withdrawal of the CBZ, with the reintroduction of the inducing drug not being considered ethical.

The principal clinical and analytical characteristics of patients with CBZ-DILE are shown in Table 1 and are compared with idiopathic SLE, "classic" DILE (due to hydralazine and procainamide), and anti-TNF- α DILE in Table 2. A significant finding that distinguishes CBZ-DILE from idiopathic SLE, classic DILE, and anti-TNF- α DILE is the absence of renal involvement. Renal disease is uncommon in DILE, unlike SLE, although cases of renal involvement have been reported after treatment with different agents, including hydralazine, sulfasalazine, propylthiouracil, penicillamine, and anti-TNF- α therapy (1, 2, 40). In DILE involving antiepileptic drugs, the few reported cases of renal involvement have been associated mainly with ethosuximide (41). The cause of these differences is not clear. The renal disease in DILE is most often due to a necrotizing glomerulonephritis, usually associated with P-ANCA positivity, with little or no immune complex deposition, although an immune complex-mediated glomerulonephritis can occur (40). The complement-fixing properties of the ANA generated in different situations could be important in contributing to lupus nephritis. Patients with SLE usually display complement-fixing ANA, while this feature is rarely present in DILE (42). Also, unlike in SLE, the clearance of circulating immune complexes by the reticuloendothelial system seems to be intact in DILE (43). These or other mechanisms could influence a different renal

involvement in idiopathic SLE and DILE, and among the DILE induced by different drugs. Moreover, the limited sample size may also have influenced in not finding any case of renal involvement.

The differential diagnosis between DILE and idiopathic SLE can occasionally be difficult due to the high number of drugs that can cause positive ANA and DILE, as well as the frequent presence of similar clinical signs, such as arthralgia/arthritis, fever and serositis, with positive ANA in both processes. The diagnosis is also difficult because the weak temporal relationship between starting to take the inducing drug and the appearance of lupus symptoms, with the latency period lasting for months or years. Our patient is notable for having a very long latency period, being 18 years free of any adverse effects. This was only surpassed by the case described by Wittchen *et al.* in which the clinical signs appeared 20 years after starting CBZ treatment (29). Differentiating them at clinical level is made easier in that some of the most relevant facts in idiopathic SLE, such as renal, neurological, and severe hematological involvement, are rare in DILE (2).

One of the risk factors in DILE due to hydralazine and procainamide is the dose of the drug (3, 9). In the case of CBZ, there was no relationship between the appearance of DILE and the dose of the drug employed, with cases being observed with doses from 200 mg/day, up to 1600 mg/day, but occurring in the majority of the cases described at usual doses (400-800 mg/day).

The typical ANA pattern associated with DILE is homogeneous (2, 3). The anti-histone antibodies can be found in both forms of lupus, although they are only present in 50% of patients with idiopathic SLE, whilst they are found in 75% of the DILE cases. The anti-histone antibodies are strongly associated with some forms, particularly in cases associated with procainamide, hydralazine, chlorpromazine, and quinidine, in which they were observed in up to 95% of cases. However, they are seen in a proportion less than 50% in the DILE associated with minocycline, propylthiouracil, and statins (3, 44, 45). Furthermore, anti-dsDNA antibodies and anti-extractable nuclear antigen antibodies (Sm/RNP) are rare in patients with DILE, unlike idiopathic SLE (1, 2), although anti-dsDNA antibodies are common in those DILE due to anti-TNF- α (46). It should be noted that there is a relatively low anti-histone

in patients with CBZ-DILE (75%), compared to classic DILE, as well as the increased presence of anti-dsDNA in approximately 50% of cases (Table 2). Anti-Sm/RNP antibodies were also observed in 2 cases. In the CBZ-DILE the ANA pattern should be in the middle zone between the classic DILE, due to procainamide, hydralazine, or quinidine, with an elevated presence of anti-histones and low presence of anti-dsDNA, and the DILE induced by anti-TNF- α , with a low presence of anti-histones and an increased presence of anti-dsDNA (2, 46).

DILE has been found to be associated frequently with HLA-DR4 an HLA-DR2, especially in lupus induced by hydralazine and minocycline (1, 2). HLA-DR2 was found in 3 of the 6 reported cases in whom data were available and HLA-DR4 in 2 cases. On the other hand, the HLA genetic variation is implicated in the development of specific cutaneous adverse reactions to CBZ, some showing clinical data similar to lupus. There is evidence linking the HLA-B*15:02 genotype with the risk of CBZ-induced SJS/TEN, and HLA-A*31:01 with maculopapular exanthema, DRESS syndrome, and SJS/TEN (47, 48). These HLA alleles, which have distinct ethnic and geographical distribution, have not been assessed in CBZ-DILE.

The early recognition of the disease and the withdrawal of the drug responsible are usually sufficient for the treatment in the majority DILE cases. In general, the symptoms of DILE are self-limiting once the inducing drug is removed. However, a greater severity of the clinical manifestations, the impossibility of abruptly withdraw the inducing drug, and the fact that the diagnosis is usually a posteriori, may make the treatment with corticosteroids, synthetic anti-malarials, or immunosuppressants necessary. In exceptional cases, it may be necessary to weigh up the risks and benefits before withdrawing an effective drug if there are no other effective alternatives, as was the case in which the CBZ was continued as it was considered as the only really effective drug for the diseases treated (23). The majority of DILE symptoms will disappear in a few weeks after withdrawing the inducing drug, although in the occasional patient it may take up to 1 year to completely recover. The ANA titer may take more time to return to negative (2, 8) or may not even return to negative in more than 60% of cases during the follow-up, as was observed in this series.

Considering the use of drugs associated with DILE in patients with SLE, there is little

evidence that shows the disadvantages of avoiding these drugs (38). In 1 of the cases described due to CBZ, the DILE symptoms were resolved by withdrawing the CBZ and administering oxcarbazepine (21), an analogue drug, with which the DILE cases have also been described. A conservative approach seems advisable in patients with SLE who could receive any medication implicated in producing DILE symptoms, monitoring any clinical evidence of increased activity of the disease, including the appearance of new organic signs, as well as the appropriate analytical monitoring (3).

This review has several limitations. Not all cases of drug reactions are reported, and even less published, especially when the most important clinical signs are not very spectacular, as is the case. Furthermore, the cases published in journals but not indexed in PubMed/Medline were not collected. On the other hand, the clinical information and in particular the analytic information is very varied from one case to the other, with the lack of serological data being especially notable in the first cases described. The fact of not always being able to abruptly discontinue the suspected inducing drug and/or that the patients may need other drugs for the control of their symptoms is also a clinical confounding factor, not being clear if the favorable outcome is due to one action or another. Some of the clinical pictures described could correspond to a reactivation of an idiopathic SLE, with epileptic and/or psychiatric signs being manifestations of the disease for which CBZ is used. Neuropsychiatric symptoms can be found in up to 50% of patients with idiopathic SLE (20, 49), which can precede the diagnosis of SLE by many years (1, 50). Finally, the follow-up varies a lot, with the time being very limited in some cases, and the treatment response not completely clear in other.

Conclusion

The cases of CBZ-DILE mentioned in the literature are characterized by being predominantly female, younger than 50 years, very variable latency periods, often years, and generally mild clinical symptoms dominated mainly by signs of rheumatic-type arthralgia or arthritis, several skin lesions, and general symptoms such as asthenia, feeling unwell or mild fever, and more rarely, pleuritis or pericarditis, with no renal involvement (Table 2). The ANAs were positive in all the cases in which they were measured, with anti-histone antibodies being observed in 75% and anti-dsDNA in 47.6% of the cases. The ANA remained positive after the withdrawal

of CBZ in more than 60% of cases during the follow-up.

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