Are there distinct clinical and pathological features distinguishing idiopathic from drug-induced subacute cutaneous lupus erythematosus? A European retrospective multicenter study

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Background: Clinical and pathologic criteria to distinguish drug-induced subacute lupus erythematosus (DI-SCLE) from idiopathic (I-SCLE) are controversial.

Objective: The aim of the survey was a retrospective analysis of a consistent number of iatrogenous and idiopathic SCLE cases, by means of clinical and histopathologic investigation.

Methods: Eleven European university dermatology units collected all diagnosed cases from January 2000 to December 2016. Board-certified dermatopathologists reviewed the histopathologic specimens. Statistical analysis included Student *t* test, exact test of goodness-of-fit, Fisher's exact test, and the Cochran-Mantel-Haenszel test for repeated measures.

Results: Out of 232 patients, 67 (29%) belonged to the DI-SCLE group. Patients with DI-SCLE were significantly older and reported more systemic symptoms than those with I-SCLE. No statistical differences were found for presentation pattern or serology, while histopathology showed a significant association of mucin deposition (P = .000083), direct immunofluorescence positivity for granular immunoglobulin M, and C3 deposits on the basement membrane zone (P = .0041) for I-SCLE and of leukocytoclastic vasculitis (P = .0018) for DI-SCLE.

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Limitations: This is a retrospective study.

Conclusion: An integrated clinical and immunopathologic evaluation is useful to differentiate I-SCLE from DI-SCLE. Older age at onset and more frequent systemic symptoms characterize DI-SCLE. Mucin deposition and immunofluorescence findings are found in I-SCLE, and leukocytoclastic vasculitis is found in DI-SCLE. (J Am Acad Dermatol 2019;81:403-11.)

Key words: drug-induced subacute lupus erythematosus; histopathology study; subacute lupus erythematosus.

CAPSULE SUMMARY

- Distinguishing drug-induced from idiopathic subacute lupus erythematosus is challenging, as their clinical, histopathologic, and laboratory presentation can be similar.
- Our results show that older age at onset and leukocytoclastic vasculitis are more commonly seen in drug-induced cases, and mucin deposition and positive immunofluorescence are clues to the idiopathic form.

Drug-induced lupus erythematosus (LE) is an autoimmune syndrome occurring in the setting of long-term drug exposure and resolving after discontinuation of the culprit drug.[1-5] Persistence of problems despite long-term removal of the drug is sometimes observed, and referred to as unmasked LE, which supports the view that the drug works as a triggering agent on the individual predisposition to develop the autoimmune disorder.[6]

Drug-induced LE can be classified as systemic LE, subacute cutaneous LE (SCLE), or chronic cutaneous lupus,[7] which is similar to idiopathic LE. The most frequent variant is drug-induced SCLE (DI-SCLE), with 70% to 80% of cases, first recognized in 1985 in association with hydrochlorothiazide.[8] The list of drugs has evolved over time to include several commonly used categories, such as antihypertensives, antidepressants, and proton pump inhibitors,[7-11] but the association for many active substances remains anecdotal. In fact, the causality assessment following standard pharmacovigilance scores[12] usually concludes for a possible association, because highly probable or certain association requires information on re-exposure (rechallenge). The administration of the same drug supposed to have induced an adverse effect is not usually performed for safety and ethical reasons.[13] In fact, this approach potentially exposes the patient to the risk of more severe reactions, which is acceptable only for irreplaceable life-saving medications and with the explicit consent of the patient.

Considering the limitations of the causality assessment, a definition of distinctive features for DI-SCLE, not expressed in the idiopathic disease (I-SCLE), might increase the force of the association. Recently, Marzano et al[14] suggested some clinical and immunologic hallmarks that could be used to identify DI-SCLE. That study did not confirm the previously suggested histopathologic criteria for DI-SCLE, however.[15]

The present multicenter observational study aimed to widen the collection of medical and histopathologic records, further investigating whether clinical, immunologic, or pathologic differences exist between DI-SCLE and I-SCLE.

MATERIALS AND METHODS

Eleven European dermatology units retrospectively reviewed all cases of SCLE diagnosed from January 1, 2000, to December 31, 2016. The coordinating center, responsible for all data collection and analysis, was the Dermatology Clinic of Cagliari University, which submitted the study to the local ethical independent committee of the Azienda Ospedaliero Universitaria of Cagliari for approval (code Prot. PG/2018/6063). Local institutional review board approval was not necessary for the limited number of cases, completely anonymous, collected from each participating institution.

Clinical data

Each center assigned a code to the cases, such that only the recruiting center could identify the source of the data recorded on the shared electronic sheet. Inclusion criteria were (1) clinical evidence of SCLE, (2) histopathologic findings consistent with SCLE, and (3) a dermatologist's diagnosis of SCLE. An additional criterion (4) was the absence or presence of drug exposure (history of new drug introduction within 6 months). Patients without a skin biopsy were excluded. Cases were divided into DI-SCLE and I-SCLE groups on the basis of the fourth criterion. The causality drug assessment followed the Jones

Abbreviations used:

DI-SCLE: drug-induced SCLE
I-SCLE: idiopathic SCLE
Ig: immunoglobulin
IVIG: intravenous immunoglobulin
LE: lupus erythematosus
SCLE: subacute cutaneous lupus erythematosus

algorithm,[16] a global introspection method chosen for being adaptable to the retrospective nature of the study: enough detail to be conclusive, even with little information available. It consists of 4 questions with yes/no answers, progressing from unrelated to related adverse events: (1) plausibility of time relation between drug exposure and manifestations onset; (2) exclusion of alternative explanation for the events; (3) evaluation of the response to the interruption; and (4) reintroduction of the suspected drug (dechallenge and rechallenge).

Histopathologic analysis

The pathology slides were assigned a study number, corresponding to the patient code, but blinded for the diagnosis, such that the dermatopathologists were unware of the clinical data. The following changes were evaluated: epidermal atrophy/acanthosis; hyperorthokeratosis; vacuolar degeneration at the basal-cell epidermal layer; epidermal keratinocyte necrosis/apoptosis; pattern and density of lymphocytic infiltration considering (1) superficial, junctional, and perivascular infiltrate (interface reaction pattern); (2) periadnexal involvement; and (3) superficial and deep involvement, presence of eosinophils, mucin deposition, and leukocytoclastic vasculitis.

Direct immunofluorescence was performed on the same site as that of the diagnostic biopsy, on lesional skin. From the medical chart, the nature of the immune deposits (immunoglobulin G [IgG]/IgA/IgM/C3), localization (epidermis or basement membrane zone/subepidermal blood vessels), and pattern (granular/linear) were retrieved.

Statistical analysis

Categorical variables were expressed as numbers and percentage means. The Student *t* test was used for continuous variables, the exact test of goodness-of-fit was used for single nominal variables compared with the expected values estimated on the basis of the implicit equiprobability model, the Fisher's exact test was used for dual nominal variables, and the Cochran-Mantel-Haenszel test was used to analyze whether there were consistent differences in proportion across the repeated locations. Adjustment for multiple comparison was applied by means of the Bonferroni test to avoid false positives due to chance. A P value $< .05$ was considered significant.

Table I. Demographic data of SCLE patients

Value	Total cohort n = 232	I-SCLE n = 165	DI-SCLE n = 67	Student *t* test *P* value
Female	174 (75)*	121 (73)	53 (79)	.232
Male	58 (25)	44 (27)	14 (21)	.09
Mean age, years	51.5	40.3	53.3	.007
DI-SCLE/SCLE	67/232 (28.9)			

DI, Drug-induced; *I*, idiopathic; *SCLE*, subacute cutaneous lupus erythematosus.
*Values are presented as n (%) unless otherwise noted.

RESULTS

The study cohort (Table I) consisted of 232 patients (174 women, 58 men) divided into group 1, which included 67 patients with DI-SCLE (53 women, 14 men; mean age 53.3 years), and group 2, with the remaining 165 I-SCLE patients (121 women, 44 men; mean age 40.6 years). Cases of DI-SCLE represented 28.98% of the whole cohort, with a mean age at onset 1 decade over I-SCLE patients, supported by the Student *t* test ($P = .007$).

Clinical feature analysis

In the overall cohort (Table II), almost one third of the patients presented with typical annular-polycyclic or papulosquamous lesions, followed by annular polycyclic and papulosquamous features overlap (14%); other atypical presentations, such as annular with malar rash, annular with bullae, annular with erythema multiforme, pityriasis-like, and toxic epidermal necrolysis-like were less frequent.

When the 2 groups were analyzed separately, the proportion of annular polycyclic or papulosquamous patterns remained similar, whereas atypical variants were more frequent in DI-SCLE. The Fisher's exact test showed a more frequent presence in DI-SCLE of annular distribution with bullae ($P = .023$), pityriasis-like ($P = .02$), and erythema multiform–like pattern ($P = .039$); however, the Bonferroni correction for multiple comparisons (8 hypothesis test), gave an adjusted critical value of .0062, and differences were not significant.

As shown in Table II, lesions were distributed in sun-exposed areas in 101 patients (49.5%), and 65 patients (31.9%) also presented with widespread lesions on covered areas. The DI-SCLE group showed a prevalence of widespread lesions,

Table II. Clinical features of the 2 patient groups

Value	Total cohort	Number of cases (%)		
Clinical presentation	**n (%)**	**I-SCLE (n = 126)**	**DI-SCLE (n = 63)**	***P***
Annular polycyclic	66 (34.9)	49 (38.9)	17 (26.9)	.283
Papulosquamous	64 (33.9)	44 (34.9)	20 (31.7)	.528
Overlap	27 (14.3)	21 (16.7)	6 (9.5)	.073
Annular with malar rash	9 (4.8)	6 (4.8)	3 (4.8)	.346
Annular with bullae	8 (4.2)	2 (1.6)	6 (9.5)	.023*
Annular with erythema multiforme	8 (4.2)	3 (2.4)	5 (7.9)	.068
Pityriasis-like	4 (2.1)	1 (0.8)	3 (4.8)	.02*
Toxic epidermal necrolysis-like	3 (1.6)	0 (0)	3 (48)	.039*
Involved areas	**n (%)**	**I-SCLE (n = 142)**	**DI-SCLE (n = 64)**	***P***
Sun-exposed	101 (49.5)	78 (54.9)	23 (35.9)	1
Widespread	65 (31.9)	34 (23.9)	31 (48.4)	.017*
Head-neck	14 (6.9)	8 (5.7)	6 (9.4)	.382
Upper limbs	13 (6.4)	12 (8.5)	1 (1.6)	.115
Chest	9 (4.4)	6 (4.2)	3 (4.7)	1
Back	3 (1.5)	3 (2.1)	0 (0)	.554
Lower limbs	1 (0.5)	1 (0.7)	0 (0)	1

DI, *D*rug-induced; *I*, idiopathic; *SCLE*, subacute cutaneous lupus erythematosus.
*$P < .05$; Bonferroni adjusted-critical value 0.0062 for $t_{(8)}$; 0.0071 for $t_{(7)}$ hypothesis.

Table III. Systemic symptoms and autoantibodies panel in the 2 patient groups

	Total cohort	I-SCLE	DI-SCLE	
Value	**n (%)**	**n (%)**	**n (%)**	***P***
Total of patients with symptoms	53 (22.8)	21 (12.7)	32 (47.8)	.00000005***
Arthralgia/arthritis	37 (15.9)	20 (12.1)	17 (25.4)	.017*
Raynaud phenomenon	14 (6)	9 (5.4)	5 (7.5)	.553
Xerostomia	14 (6)	6 (3.6)	8 (11.9)	.029*
Nonspecific symptoms (fever, malaise)	13 (5.6)	8 (4.8)	5 (7.5)	.529
Xerophthalmia	9 (3.9)	4 (2.4)	5 (7.5)	.125
Nephropathy	7 (3)	3 (1.8)	4 (6)	.109
Serositis	0 (0)	0 (0)	0 (0)	1
Autoantibody panel	**No. tot tests**	**I-SCLE No. pos /tot (%)**	**DI-SCLE No. pos/tot (%)**	***P***
ANA	178	83/121 (68.6)	47/57 (82.4)	.07
ENA	176	80/119 (67.2)	42/57 (73.7)	.485
Ro/SS-A	158	68/102 (42.1)	39/56 (69.6)	.726
La/SS-B	146	23/91 (25.3)	14/55 (25.4)	1.00
dsDNA	137	12 /93(12.9)	4/44 (9.1)	.584
Anti-Sm	129	6/77 (7.8)	4/52(7.7)	1.00
LAC	94	7/54 (13)	2/40 (5)	.293
Antihistone	85	6/45 (13.3)	9/40 (22.5)	.393

*$P < .05$; *** $P < .01$; Bonferroni adjusted-critical value 0.0071 for $t_{(7)}$ hypothesis.
ANA, Antinuclear antibody; *DI*, drug-induced; ENA, extractable nuclear antigen; *I*, idiopathic; *pos*, positive; *SCLE*, subacute cutaneous lupus erythematosus; *tot*, total.

supported by Fisher's exact test ($P = .017$), but not after the Bonferroni correction (7 hypothesis test) that adjusted the critical value to .0071.

Systemic symptoms were present in 53 patients (27%) (Table III), with prevalence in DI-SCLE patients supported by a highly significant Fisher's exact test result.

Arthralgia/arthritis was the most frequent symptom in both groups (12.1% in I-SCLE, 25.4% in DI-SCLE), followed by Raynaud phenomenon and nonspecific symptoms such as fever and malaise. The DI-SCLE group had a greater number of reported xerostomia (11.9%) and nephropathy (6%) cases compared with the I-SCLE group. However, a

comparison of the single symptoms showed no significance because of the small numbers in both groups.

The search for autoantibodies was the most variable finding among the participating centers, with limited number of patients tested (Table III). The most performed testing was for antinuclear antibody titer with a positivity slightly in favor of DI-SCLE (82.4% instead of 68.6%), and extractable nuclear antigen screening, which did not show any difference among the groups. Analysis for anti-Ro/SS-A was performed in 158 patients overall, with a slight prevalence in DI-SCLE (69.6% positive vs 42.1% of I-SCLE). Antihistone was tested in 85 patients, with similar positivity in both groups. Neither the Fisher's exact test nor the Cochran-Mantel-Haenszel test showed significant differences between the 2 groups.

Culprit drugs included 76 molecules, with contemporary exposure to 2 to 4 active substances in some patients (Table IV). Diuretics were the most represented class (11.8%), followed by biologics, cardiologics, and chemotherapies (10.5%). The top single active substance was hydrochlorothiazide, followed by leflunomide, estroprogestinics, and terbinafine. The application of the Jones algorithm revealed 4 (5%) active principles (carboplatin, gemcitabine, lamotrigine, desloratadine) with a certain association, while a causal relation was probable for 25 drugs (33%) and possible for the remaining substances (62%).

Histopathologic analysis and direct immunofluorescence findings

No differences between the two groups (Table V) were found except for epidermal acanthosis (P = .024), keratinocyte necrosis/apoptosis (P = .017), cytoid bodies (P = .018), mucin deposition (P = .000005), and leukocytoclastic vasculitis (P = .00013). Adjustment for an 11 hypothesis test (Bonferroni) gave a critical value of .0045, and the statistical significance was confirmed only for mucin deposition (odds ratio 2.28) in favor of I-SCLE and leukocytoclastic vasculitis (odds ratio 0.118) in favor of DI-SCLE.

Data on direct immunofluorescence were available in 133 of 232 cases (57%) (Table V), and the most relevant difference was the combined presence of C3c and IgM at the dermoepidermal junction in 52.2% of I-SCLE patients versus 20.9% of DI-SCLE patients. The finding was statistically significant, with an odds ratio of 1.093 in favor of I-SCLE.

DISCUSSION

The association between drug intake and the occurrence of SCLE has been increasingly reported and poses the problem of the risk's evaluation for the general population exposed to certain active substances or categories of drugs. A recent Denmark survey estimated that DI-SCLE accounts for 20% of all SCLE cases,[17] and other authors suggested that the condition might occur more frequently than that reported.[9] The present multicenter study largely confirms these findings, as 29% of our patients fulfilled the criteria for DI-SCLE, suggesting that for every 4 patients with SCLE, 1 possibly has drug-induced disease. The literature concerning the criteria to identify DI-SCLE as a separate entity from I-SCLE is still unclear. A systematic review concluded that DI-SCLE does not differ clinically, histopathologically, or immunologically from I-SCLE.[15] However, Marzano et al observed that the age at disease onset was higher in patients with DI-SCLE than in those with I-SCLE,[14] and our data concurred, with a decade between patients with I-SCLE and DI-SCLE and a significant P value (Table I). This finding has been hypothesized to be consistent with the increasing frequency and number of co-medications with age.[15] Other suggested criteria include a more heterogeneous widespread clinical presentation, involving areas usually spared by I-SCLE,[14] with bullous and erythema multiform–like patterns, as well as the presence of systemic LE–like malar rash, purpura, and necrotic-ulcerative lesions.[14,18-22] In contrast, the prevalence of systemic involvement was considered characteristic of I-SCLE.[23-25] We could not confirm these individual criteria, as we found no significant differences in clinical presentation, pattern, and distribution of lesions, while systemic symptoms as a whole were almost 4 times more frequent in the DI-SCLE group than in the I-SCLE group (Table III). However, when performing the analysis for a single symptom, there were no statistical differences between the 2 groups. A possible explanation for this apparently contrasting evidence is that a wider spectrum of symptoms, not just cutaneous, are reported in DI-SCLE, probably related to older age or comorbidities.

Although the low number of patients tested could make conclusions not accurate, the serologic profile in most of our patients was in line with literature findings for SCLE,[11,14,15,26] including positivity for antinuclear antibody associated with anti-Ro/SS-A antibodies, without significant differences between DI-SCLE and I-SCLE.

Few studies have compared the different pathologic features of drug-induced and idiopathic SCLE. Marzano et al[14] provided a description of DI-SCLE histopathologic findings, with no attempt to describe the differences from I-SCLE. Other studies have suggested an increased positive dust-like granular

Table IV. List of drugs and causality assessment according to the Jones algorithm

				Algorithm of Jones		
Drug category	**No. of cases (%)**	**Active principle**	**n**	**Certain**	**Probable**	**Possible**
Diuretics	9/76 (11.8)	Hydrochlorothiazide	8	0	2	6
		Furosemide	1	0	0	1
Biologics	8/76 (10.5)	Etanercept	2	0	0	2
		Adalimumab	1	0	0	1
		Infliximab	1	0	0	1
		Rituximab	1	0	0	1
		Nivolumab	1	0	0	1
		Bevacizumab	1	0	1	0
		Certolizumab	1	0	0	1
Cardiologics	8/76 (10.5)	Amlodipine	2	0	0	2
		Nitrendipine	1	0	1	0
		Ramipril	1	0	1	0
		Enalapril	1	0	1	0
		Bisoprolol	1	0	0	1
		Irbesartan	1	0	0	1
		Flecainide	1	0	0	1
Chemotherapies	8/76 (10.5)	Gemcitabine	2	1	0	1
		Capecitabine	2	0	0	2
		Carboplatin	2	1	0	1
		Cisplatin	1	0	0	1
		Docetaxel	1	0	0	1
Nonsteroid anti-inflammatories	7/76 (9.2)	Ibuprofen	1	0	1	0
		Nimesulide	1	0	1	0
		Diclofenac	1	0	1	0
		Paracetamol	1	0	1	0
		Acetylsalicylic acid	1	0	1	0
		Naproxen	1	0	1	1
		Piroxicam	1	0	0	1
Immunomodulatory	6/76 (7.9)	Leflunomide	4	0	1	3
		Intravenous immunoglobulins	1	0	0	1
		Interferon-α	1	0	0	1
Antibiotics/antifungals	5/76 (6.6)	Terbinafine	3	0	1	2
		Doxycycline	1	0	1	0
		Amoxicillin clavulinate	1	0	1	0
Antiplatelets/anticoagulants	4/76 (5.3)	Cardioaspirin	1	0	0	1
		Rivaroxaban	1	0	0	1
		Dabigatran	1	0	0	1
		Prasugrel	1	0	0	1
Proton pump inhibitors	4/76 (5.3)	Omeprazole	2	0	0	2
		Lansoprazole	1	0	0	1
		Pantoprazole	1	0	0	1
Hormones	4/76 (5.3)	Estroprogestinics	4	0	2	2
Antiepileptics	3/76 (3.9)	Lamotrigine	1	1	0	0
		Carbamazepine	1	0	1	0
		Oxcarbazepine	1	0	1	0
Psychotropics	3/76 (3.9)	Bromazepam	1	0	0	1
		Paroxetine	1	0	0	1
		Fluvoxamine	1	0	0	1
Antimalarials	2/76 (2.6)	Hydroxychloroquine	2	0	2	0
Uricosurics	2/76 (2.6)	Allopurinol	2	0	1	1
Hypolipidemic	2/76 (2.6)	Rosuvastatin	1	0	0	1
		Ezetimibe	1	0	1	0
Antihistamines	1/76 (1.3)	Desloratadine	1	1	0	0
Final causality assessment				4 (5%)	25 (33%)	47 (62%)

Table V. Histologic features and direct immunofluorescence panel in the 2 patient groups

Histologic feature	Total cohort n (%)	I-SCLE (n = 164) n (%)	DI-SCLE (n = 66) n (%)	Observed *P*
Epidermal atrophy	149 (64.8)	105 (64)	44 (66.7)	.761
Epidermal hyperplasia	35 (15.2)	19 (11.6)	16 (24.2)	.024*
Keratinocyte necrosis/apoptosis	138 (59.5)	90 (54.9)	48 (72,8)	.017*
Hyper/orthokeratosis	76 (33)	51 (31.1)	25 (37.9)	.354
Vacuolar degeneration	206 (89.6)	149 (90,8)	57 (86.4)	.343
Perivascular lymphocytic infiltrate	225 (97.8)	161 (98.2)	64 (97)	.627
Periadnexal lymphocytic infiltrate	120 (52.2)	91 (55.5)	29 (43.4)	.144
Cytoid bodies in the dermis	58 (25.2)	34 (20.7)	24 (36.4)	.018*
Eosinophils	14 (6)	9 (5.5)	5 (7.6)	.551
Mucin deposition	138 (60)	114 (69.5)	24 (36.4)	.000005***
Leukocytoclastic vasculitis	7 (3)	0 (0)	7 (10.6)	.00013***
Direct immunofluorescence	**Tot. cohort n (%)**	**I-SCLE (n = 90) n (%)**	**DI-SCLE (n = 43) n (%)**	***P***
IgG alone	4 (3)	2 (2.2)	2 (4.7)	.594
IgM alone	7 (5.3)	6 (6.7)	1 (2.3)	.427
C3c alone	5 (3.7)	3 (3.3)	2 (4.7)	.658
IgG + C3c	7 (5.3)	3 (3.3)	4 (9.3)	.212
IgM + C3c	56 (42.1)	47 (52.2)	9 (20.9)	.00069***
IgG + IgM + C3c	13 (9.8)	9 (10)	4 (9.3)	1.00

*$P < .05$; ***$P < .01$; Bonferroni adjusted-critical value 0.0045 for $t_{(11)}$ hypothesis.
DI, Drug-induced; *I*, idiopathic; *Ig*, immunoglobulin; *SCLE*, subacute cutaneous lupus erythematosus.

IgG deposition along the basement membrane zone in DI-SCLE.[27-29] The first author to propose distinctive microscopic clues, such as tissue eosinophilia, was Callen.[10] In our study, no significant differences were found in the mean eosinophil content, basal cell vacuolar liquefaction, keratinocyte necrosis, and depth and pattern of inflammatory infiltration. The only significant associations were with mucin deposition in the dermis and positive direct immunofluorescence for both IgM and C3c along the basement membrane zone in I-SCLE, and the presence of leukocytoclastic vasculitis in DI-SCLE.

The pathogenesis of DI-SCLE remains unresolved, but active principles or their metabolites probably unchain the autoreactive process, superimposable to the idiopathic disease, in a predisposed individual carrying the HLA-DR3 antigen. Many drugs, primarily hydrochlorothiazide, are potential photosensitizers, and others interfere with the immune balance or induce an enzymatic and endocrine dysregulation, favoring the loss of self-tolerance against cell nuclei antigens.[8,30-32]

Our study included patients with many of the associated drugs as reported elsewhere[1-7,17,31-39]: hydrochlorothiazide, terbinafine and biologics, especially TNFα antagonists, antiepileptics, and proton pump inhibitors. Additional drugs frequently associated with DI-SCLE include nonsteroidal anti-inflammatory drugs and antihypertensive drugs, such as calcium channel blockers and angiotensin-converting enzyme inhibitors.[39-43] The second most frequent active substance in our study was leflunomide, an immune-modulating agent that suppresses the production of proinflammatory cytokines, especially TNFα, with a mechanism similar to modern anti-TNFα biologic drugs. Only 3 cases of leflunomide DI-SCLE were retrieved in prior reviews of the MEDLINE database,[20,44,45] and we report 4 more cases. At least 2 other culprit agents deserve attention, because of a sort of paradoxic reaction: certolizumab-pegol and intravenous immunoglobulins (IVIGs). Literature retrieval found no previous reports of SCLE certolizumab-pegol induction, and surprisingly, the switch to this fusion-humanized protein was indicated in patients with inflammatory bowel diseases who developed lupus-like symptoms from anti-TNFα.[46] As for IVIG, considered among therapeutic options for patients with severe resistant LE cases,[47] there is a 6-case series of disseminated cutaneous LE induced by IVIG.[48]

The causality assessment of adverse drug reactions is a multistep process, based on 4 cardinal principles: temporal relationship, biological plausibility, amelioration after withdrawal (dechallenge), and worsening after rechallenge. Several causality assessment tools support the clinician in the correlation judgment,[13] and the adoption of the Jones algorithm[16] in our study identified 4 drugs (5%) with a certain association, 3 of which are associated with previous reports (gemcitabine, carboplatin, and lamotrigine) and another (desloratadine) not currently listed, which warrants further evaluation.

A final judgment of a probable association characterized 25 active substances (32%), including hydrochlorothiazide, several cardiologics, anti-inflammatory drugs, hydroxychloroquine, and terbinafine. For all other drugs (62%), the association remained only possible. If confirmed by other prospective studies, the histopathology assessment might be a useful criterion for implementing DI-SCLE diagnostic accuracy and causality judgment.

Discontinuation of the culprit drug remains the major therapeutic intervention in any adverse drug reaction, including DI-SCLE, which, unlike I-SCLE, usually results in recovery within 8 to 12 weeks,[14,17,39] although Ro/SSa antibodies might remain positive for months or even years.[15] Persistence of problems despite long-term removal of the drug, namely, drug-unmasked LE, and other refractory cases might require pharmacologic treatment.[6] Systemic corticosteroids are supplied at doses commonly used for I-SCLE, followed by antimalarials, and other immunosuppressants, such as azathioprine, thalidomide, or mycophenolate-mofetil. Topical steroids have also been used with variable success.[49]

The present survey was not expressly designed to give information about long-term monitoring, but all cases improved at dechallenge, and none of the centers reported persistence of manifestations after definite withdrawal.

CONCLUSION

Over the last decade, the awareness that a distinct subset of subacute LE might be associated with drugs challenged the definition of clinical and laboratory features that are useful to differentiate DI-SCLE from its idiopathic counterpart, with contradictory findings. The present multicenter study found minimal but significant differences in clinical features, such as age at onset and nonspecific systemic complaints, and histopathologic findings. Mucin deposition and IgM and C3 positivity at the basement membrane zone were microscopic clues of I-SCLE, and leukocytoclastic vasculitis was a clue of DI-SCLE. The multistep drug causality assessment might benefit from the integrated evaluation of additional clinical, histopathologic, and immunofluorescence findings to support a DI-SCLE diagnosis.

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