

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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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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66 histopathology study.

67 **Abstract**

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

70 *Objective:* Aim of the survey was a retrospective analysis of a consistent number of iatrogenous
71 and idiopathic SCLÉ cases, by means of clinical and histopathological investigation.

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

76 *Results:* Out of 232 patients, 67 (29%) belonged to the DI-SCLÉ group. Patients with DI-
77 SCLÉ were significantly older and complained more systemic symptoms than those with I-SCLÉ.
78 No statistical differences were found for presentation pattern or serology, while histopathology
79 showed for I-SCLÉ a significant association of mucin deposition ($p=0,000083$) and direct
80 immunofluorescence positivity for granular IgM, C3 deposits on the basement membrane zone
81 ($p=0,0041$), and of leukocytoclastic vasculitis ($p=0,0018$) for DI-SCLÉ.

82 *Limitations:* This is a retrospective study.

83 *Conclusion:* An integrated clinical and immunopathological evaluation is useful to differentiate
84 I-SCLÉ from DI-SCLÉ. Older age at onset and more frequent systemic symptoms characterize DI-
85 SCLÉ. Mucin deposition and immunofluorescence findings are found in I-SCLÉ, while
86 leukocytoclastic vasculitis in DI-SCLÉ.

87

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89

90 **Introduction**

91 Drug-induced lupus erythematosus (DI-LE) is an autoimmune syndrome occurring in the setting
92 of chronic drug exposure and resolving after discontinuation of the culprit drug (1-5).

93 Persistence despite long-term removal of the drug is sometimes observed, and referred as
94 unmasked LE, which support the view that the drug works as a triggering agent on the
95 individual predisposition to develop the autoimmune disorder (6).

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

108 Considering the limitations of the causality assessment, definition of distinctive features for the
109 drug-induced SCLE, not expressed in the idiopathic disease (I-SCLE) might increase the force of
110 the association. Recently, Marzano et al. (14) suggested some clinical and immunological

111 hallmarks that could be used to identify DI-SCLE. However, the study did not confirm the
112 previously suggested histopathologic criteria for DI-SCLE (15).

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

116

117 **Materials and Methods**

118 Eleven European Dermatology units retrospectively reviewed all cases of SCLE diagnosed from
119 January 1, 2000 to December 31, 2016. The Coordinating center, responsible for all data
120 collection and analysis was the Dermatology Clinic of Cagliari University, which submitted the
121 study to the local Ethical Independent Committee of the AOU of Cagliari for approval (code
122 Prot. PG/2018/6063). Local IRB approval was not necessary for the limited number of cases,
123 completely anonymous, collected from each participating Institution.

124 Clinical data

125 Each center assigned a code to the cases, such that only the recruiting center could identify the
126 source of the data recorded on the shared electronic sheet. Inclusion criteria were: (I) clinical
127 evidence of SCLE, (II) histopathological findings consistent with SCLE, and (III) a dermatologist's
128 diagnosis of SCLE. An additional criterion (IV) was the absence/presence of drug exposure
129 (history of new drug introduction within 6 months). Patients without a skin biopsy were
130 excluded. Cases were divided into DI-SCLE and I-SCLE groups on the base of the IV criterion. The
131 causality drug assessment followed the Jones algorithm (16), a global introspection method
132 chosen for being adaptable to the retrospective nature of the study: enough detailed to be

133 conclusive, even with few information available. It consists of 4 questions with yes or no
134 answers, progressing from unrelated to related adverse events: 1- plausibility of time relation
135 between drug exposure and manifestations onset; 2- exclusion of alternative explanation for
136 the events; 3- evaluation of the response to the interruption and 4- reintroduction of the
137 suspected drug (dechallenge and rechallenge).

138 Histopathologic analysis

139 The pathology slides were assigned a study number, corresponding to the patient code, but
140 blinded for the diagnosis, such that the dermatopathologists were unaware of the clinical data.
141 The following changes were evaluated: 1, epidermal atrophy/acanthosis; 2, hyper-
142 orthokeratosis; 3, vacuolar degeneration at the basal-cell epidermal layer; 4, epidermal
143 keratinocyte necrosis/apoptosis; 5, pattern and density of lymphocytic infiltration considering
144 (a) superficial, junctional, and perivascular infiltrate (interface reaction pattern), (b) Periadnexal
145 involvement, and (c) superficial and deep involvement; 6, presence of eosinophils; 7, mucin
146 deposition; 8, leukocytoclastic vasculitis.
147 Direct immunofluorescence (DIF) was performed on the same site of the diagnostic biopsy, on
148 lesional skin. From the medical chart, the nature of the immune deposits (IgG/IgA/IgM/C3),
149 localization (epidermis or basement membrane zone [BMZ]/sub epidermal blood vessels), and
150 pattern (granular/linear) were retrieved.

151 Statistical analysis

152 Categorical variables were expressed as numbers and percentage means. The Student's t-test
153 was used for continuous variables; the exact test of goodness-of-fit for single nominal variables
154 compared to the expected values estimated on the basis of the implicit equiprobability model;

155 the Fisher's exact test for dual nominal variables, and Cochran–Mantel–Haenszel test to analyze
156 if there were consistent differences in proportion across the repeated locations. Adjustment for
157 multiple comparison was applied by mean of the Bonferroni test, to avoid false positives due to
158 chance. A p-value <0.05 was considered significant.

159

160 **Results**

161 The study cohort (Table 1) consisted of 232 patients, 174 women, and 58 men divided into
162 group 1, which included 67 patients with DI-SCLE (53 woman, 14 men; mean age, 53.3 years),
163 and group 2 with the remaining 165 I-SCLE patients (121 women, 44 men; mean age, 40.6
164 years). Cases of DI-SCLE represented 28.98% of the whole cohort, with a mean age at onset one
165 decade over I-SCLE patients, supported by Student's t test (p 0.007).

166 Clinical feature analysis

167 In the overall cohort (Table 2), almost one-third of the patients presented with typical annular-
168 polycyclic or papulosquamous lesions, followed by annular polycyclic and papulosquamous
169 features overlap (14%); other atypical presentations, such as annular with malar rash, annular
170 with bullae, annular with erythema multiforme, pityriasis-like and toxic epidermal necrolysis-
171 like were less frequent.

172 When the two groups were analyzed separately, the proportion of annular polycyclic or
173 papulosquamous patterns remained similar, while atypical variants were more frequent in DI-
174 SCLE. The Fisher's exact test showed a more frequent presence in DI-SCLE of annular
175 distribution with bullae (p=0.023), pityriasis-like (p=0.02), and erythema multiform-like pattern

176 (p=0.039); however, the Bonferroni correction for multiple comparisons (eight hypothesis test),
177 gave an adjusted-critical value of 0.0062, and differences were not significant.

178 As shown in Table 2, lesions were distributed in sun-exposed areas in 101 patients (49.5%),
179 while 65 patients (31.9%) also presented with widespread lesions on covered areas. The DI-
180 SCLE group showed a prevalence of widespread lesions, supported by Fisher's exact test
181 (p=0.017), but not after the Bonferroni correction (seven hypothesis test), that adjusted the
182 critical value to 0.0071.

183 Systemic symptoms were present in 53 patients (27%) (Table 3), with prevalence in DI-SCLE
184 patients supported by highly significant Fisher's exact test.

185 Arthralgia/arthritis was the most frequent symptom in both groups (12.1% in I-SCLE, 25.4% in
186 DI-SCLE), followed by Raynaud phenomenon, and non-specific symptoms such as fever and
187 malaise. The DI-SCLE group had a greater number of reported xerostomia (11.9%) and
188 nephropathy (6%) compared to the I-SCLE group. However, a comparison of the single
189 symptoms showed no significance because of the small numbers in both groups.

190 The search of autoantibodies was the most variable finding among the participating centers,
191 with limited number of patients tested (Table 3). The most performed testing was for
192 antinuclear antibody (ANA) titer with a positivity slightly in favor of DI-SCLE (82.4% instead of
193 68.6%), and extractable nuclear antigens (ENA) screening, which did not show any difference
194 among the groups. Analysis for anti-Ro/SSA was performed in 158 patients overall, with a slight
195 prevalence in DI-SCLE (69.6% positive versus 42.1% of I-SCLE). Anti-histone was tested in 85
196 patients, with similar positivity in both groups. Neither the Fisher's exact test nor the Cochran-
197 Mantel-Haenszel test showed significant differences between the two groups.

198 Culprit drugs included 76 molecules, with contemporary exposure to two/four active
199 substances in some patients (Table 4). Diuretics were the most represented class (11.8%),
200 followed by biologics, cardiologics, and chemotherapies (10.5%). The top single active
201 substance was hydrochlorothiazide, followed by leflunomide, estro-progestinics, and
202 terbinafine. The application of the Jones' algorithm revealed four (5%) active principles
203 (carboplatin, gemcitabine, lamotrigine, desloratadine) with a certain association, while a causal
204 relation was probable for 25 drugs (33%) and possible for the remaining substances (62%).

205 Histopathologic analysis and direct immunofluorescence findings

206 No differences between the two groups (Table 5) were found except for epidermal acanthosis
207 ($p=0.024$), keratinocyte necrosis/apoptosis ($p=0.017$), cytooid bodies ($p=0.018$), mucin
208 deposition ($p=0.000005$), and leukocytoclastic vasculitis ($p=0.00013$). However, adjustment for
209 eleven hypothesis test (Bonferroni) gave a critical value of 0.0045, and the statistical
210 significance was confirmed only for mucin deposition (odds ratio [OR] 2.28) in favor of I-SCLE,
211 and leukocytoclastic vasculitis (OR: 0.118) in favor of DI-SCLE.

212 Data on direct immunofluorescence were available in 133 of 232 cases (57%) (Table 5), and the
213 most relevant difference was the combined presence of C3c and IgM at the dermo-epidermal
214 junction in 52.2% of I-SCLE patients vs 20.9% of DI-SCLE. The finding was statistically significant,
215 with an OR of 1.093 in favor of I-SCLE.

216

217 **Discussion**

218 The association between drug intake and the occurrence of SCLE has been increasingly
219 reported, and poses the problem of the risk's evaluation for the general population, exposed to

220 certain active substances or categories of drugs. A recent Denmark survey estimated that DI-
221 SCLE accounts for 20% of all SCLE cases (17), and other authors suggested that the condition
222 might occur more frequently than that reported (9). The present multicenter study largely
223 confirms these findings, as 29% of our patients fulfilled the criteria for DI-SCLE, suggesting that
224 for every four patients with SCLE, one possibly has a drug-induced disease. The literature
225 concerning the criteria to identify DI-SCLE as a separate entity from I-SCLE is still unclear. A
226 systematic review concluded that DI-SCLE does not differ clinically, histopathologically, or
227 immunologically from I-SCLE (15). However, Marzano et al (14) observed that the age at disease
228 onset was higher in patients with DI-SCLE compared with those with I-SCLE, and our data
229 concurred, with a decade between patients with I-SCLE and DI-SCLE, and a significant p-value
230 (Table 1). This finding has been hypothesized to be consistent with the increasing frequency
231 and number of co-medications with age (15). Other suggested criteria include a more
232 heterogeneous widespread clinical presentation, involving areas usually spared by I-SCLE (14),
233 with bullous and erythema multiform-like patterns, as well as the presence of SLE-like malar
234 rash, purpura, and necrotic-ulcerative lesions (14, 18-22). In contrast, the prevalence of
235 systemic involvement was considered characteristic of I-SCLE (23-25). We could not confirm
236 these individual criteria, as we found no significant differences in clinical presentation, pattern,
237 and distribution of lesions, while systemic symptoms as a whole were almost four times more
238 frequent in the DI-SCLE group than in the I-SCLE (Table 3). However, by performing the analysis
239 for single symptom, there were no statistical differences between the two groups. A possible
240 explanation for this apparently contrasting evidence is that a wider spectrum of symptoms, not
241 just cutaneous are reported in DI-SCLE, probably related to older age or comorbidities.

242 Although the low number of patients tested could make conclusions not accurate, the
243 serological profile in most of our patients was in line with literature findings for SCLE (11, 14-15,
244 29), including ANA positivity associated with anti-Ro/SSA antibodies, without significant
245 differences between DI-SCLE and I-SCLE.

246 Few studies compared the different pathologic features of drug-induced and idiopathic SCLE.
247 Marzano et al (14) provided a description of DI-SCLE histopathologic findings, with no attempt
248 to describe the differences from I-SCLE. Other studies suggested an increased positive dust-like
249 granular IgG deposition along the basement membrane zone in DI-SCLE (28,29). The first author
250 to propose distinctive microscopic clues, such as tissue eosinophilia, was Callen (10). In our
251 study, no significant differences were found in the mean eosinophil content, basal cell vacuolar
252 liquefaction, keratinocyte necrosis, depth and pattern of inflammatory infiltration. The only
253 significant associations were with mucin deposition in the dermis and positive direct
254 immunofluorescence for both IgM and C3c along the basement membrane zone in I-SCLE, and
255 the presence of leukocytoclastic vasculitis in DI-SCLE.

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

262 Our study included patients with many of the associated drugs as reported elsewhere (1-7, 17,
263 31-39): hydrochlorothiazide, terbinafine and biologics, especially TNF α antagonists, anti-

264 epileptics, and proton pump inhibitors. Additional drugs frequently associated with DI-SCLE
265 include non-steroidal anti-inflammatory drugs and antihypertensive drugs, such as calcium
266 channel blockers and angiotensin-converting enzyme inhibitors (39-43). The second most
267 frequent active substance in our study was leflunomide, an immune-modulating agent that
268 suppresses the production of pro-inflammatory cytokines, especially TNF α , with a mechanism
269 similar to modern anti-TNF α biologic drugs. Only 3 cases of leflunomide DI-SCLE were retrieved
270 in prior Medline database (20, 44, 45), and we report 4 more cases. At least two other culprit
271 agents deserve attention, because of a sort of paradoxical reaction: certolizumab-pegol and
272 intravenous immunoglobulins (IVIg). Literature retrieval found no previous reports of SCLE
273 certolizumab-pegol induction, and surprisingly, the switch to this fusion-humanized protein was
274 indicated in patients with inflammatory bowel diseases who developed lupus-like symptoms
275 from anti-TNF α (46). As for IVIg, considered among therapeutic options for patient with severe
276 resistant LE cases (47), there is a six cases series of disseminated cutaneous LE induced by IVIg
277 (48).

278 The causality assessment of adverse drug reactions is a multistep process, based on four
279 cardinal principles: temporal relationship, biological plausibility, amelioration after withdrawal
280 (dechallenge), and worsening after rechallenge. Several causality assessment tools (CATs)
281 support the clinician in the correlation judgement (13), and the adoption of the Jones algorithm
282 (16) in our study identified four drugs (5%) with a certain association, three of which with
283 previous reports (gemcitabine, carboplatin, and lamotrigine), and another (desloratadine) not
284 currently listed, which warrants further evaluation. A final judgment of a probable association
285 characterized 25 active substances (32%), including hydrochlorothiazide, several cardiologics,

286 anti-inflammatory drugs, hydroxychloroquine, and terbinafine. For all other drugs (62%), the
287 association remained only possible. If confirmed by other prospective studies, the
288 histopathology assessment might be a useful criterion for implementing DI-SCLE diagnostic
289 accuracy and causality judgment.

290 Discontinuation of the culprit drug remains the major therapeutic intervention in any adverse
291 drug reaction, including DI-SCLE, which, unlike idiopathic SCLE, usually result in recovery within
292 8 to 12 weeks (14, 17, 39), although Ro/SSa antibodies might remain positive for months or
293 even years (15). Persistence of clinical manifestations despite long-term removal of the drug,
294 namely drug unmasked LE, and other refractory cases might require pharmacological treatment
295 (6). Systemic corticosteroids are supplied at doses commonly used for I-SCLE, followed by
296 antimalarials, and other immunosuppressants, such as azathioprine, thalidomide, or
297 mycophenolate-mofetil. Topical steroids have also been used with variable success (49).

298 Present survey was not expressively designed to give information about long-term monitoring,
299 but all cases improved at dechallenge, and none of the centers reported persistence of
300 manifestations after definite withdrawal.

301

302 **Conclusions**

303 Over the last decade, the awareness that a distinct subset of subacute lupus erythematosus
304 might be associated with drugs challenged the definition of clinical and laboratory features that
305 are useful to differentiate DI-SCLE from its idiopathic counterpart, with contradictory findings.
306 The present multicenter study found minimal, but significant differences in clinical features,
307 such as age at onset and non-specific systemic complaints, and histopathological findings.

308 Mucin deposition and IgM and C3 positivity at the basement membrane zone were microscopic
309 clues of I-SCLE, while leukocytoclastic vasculitis of DI-SCLE. The multistep drug causality
310 assessment might benefit of the integrated evaluation of additional clinical, histopathological
311 and immunofluorescence findings, which support DI-SCLE diagnosis.

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438 **Table legends**439 **Table 1.** Demographic data of SCLÉ patients

	Total cohort N=232	I-SCLÉ N=165	DI-SCLÉ N= 67	Student's t-test p-value
Female	174 (75%)	121 (73%)	53 (79%)	0.232
Male	58 (25%)	44 (27%)	14 (21%)	0.09
Age (mean)	51.5	40.3	53.3	0.007
DI-SCLÉ/SCLE	67/232 (28.9%)			

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454 **Table 2.** Clinical features of the two patients' groups

Clinical presentation	Tot. cohort	N° of cases (%)		p-value
	N (%)	I-SCLE (n=126)	DI-SCLE (n=63)	
Annular polycyclic	66 (34.9)	49 (38.9)	17 (26.9)	0.283
Papulosquamous	64 (33.9)	44 (34.9)	20 (31.7)	0.528
Overlap	27 (14.3)	21 (16.7)	6 (9.5)	0.073
Annular with malar rash	9 (4.8)	6 (4.8)	3 (4.8)	0.346
Annular with bullae	8 (4.2)	2 (1.6)	6 (9.5)	0.023*
Annular with erythema multiforme	8 (4.2)	3 (2.4)	5 (7.9)	0.068
Pityriasis-like	4 (2.1)	1 (0.8)	3 (4.8)	0.02*
Toxic Epidermal Necrolysis-like	3 (1.6)	0 (0)	3 (4.8)	0.039*
Involved areas	N (%)	I-SCLE (n=142)	DI-SCLE (n=64)	p-value
Sun-exposed	101 (49.5)	78 (54.9)	23 (35.9)	1
Widespread	65 (31.9)	34 (23.9)	31 (48.4)	0.017*
Head-neck	14 (6.9)	8 (5.7)	6 (9.4)	0.382
Upper limbs	13 (6.4)	12 (8.5)	1 (1.6)	0.115
Chest	9 (4.4)	6 (4.2)	3 (4.7)	1
Back	3 (1.5)	3 (2.1)	0 (0)	0.554
Lower limbs	1 (0.5)	1 (0.7)	0 (0)	1

* $p < 0.05$; Bonferroni adjusted-critical value 0.0062 for $t_{(8)}$; 0.0071 for $t_{(7)}$

hypothesis.

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456 **Table 3.** Systemic symptoms and autoantibodies panel in the two patients' groups

	Total cohort	I-SCLE	DI-SCLE	
	N (%)	N (%)	N (%)	p-value
Total of patients with symptoms	53 (22.8)	21 (12.7)	32 (47.8)	0.00000005***
Arthralgia/Arthritis	37 (15.9)	20 (12.1)	17 (25.4)	0.017*
Raynaud phenomenon	14 (6)	9 (5.4)	5 (7.5)	0.553
Xerostomia	14 (6)	6 (3.6)	8 (11.9)	0.029*
Non-specific symptoms (fever, malaise)	13 (5.6)	8 (4.8)	5 (7.5)	0.529
Xerophthalmia	9 (3.9)	4 (2.4)	5 (7.5)	0.125
Nephropathy	7 (3)	3 (1.8)	4 (6)	0.109
Serositis	0 (0)	0 (0)	0 (0)	1
Autoantibodies panel		I-SCLE	DI-SCLE	
	N° tot tests	N°pos /tot (%)	N°pos/tot (%)	p-value
ANA	178	83/121 (68.6)	47/57 (82.4)	0.07
ENA	176	80/119 (67.2)	42/57 (73.7)	0.485
Ro/SSA	158	68/102 (42.1)	39/56 (69.6)	0.726
La/SSB	146	23/91 (25.3)	14/55 (25.4)	1.00
dsDNA	137	12 /93(12.9)	4/44 (9.1)	0.584
anti-SM	129	6/77 (7.8)	4/52(7.7)	1.00

LAC	94	7/54 (13)	2/40 (5)	0.293
anti-histone	85	6/45 (13.3)	9/40 (22.5)	0.393
* p-value < 0.05; *** p-value < 0.01; Bonferroni adjusted-critical value 0.0071 for t₍₇₎ hypothesis.				

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458 **Table 4.** List of drugs and causality assessment according to the Jones' algorithm.

Drug Categories	Cases (%)	Active principle	N	Algorithm of Jones		
				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
Non-steroid anti-inflammatory 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
	IV-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 (PPI) 4/76 (5.3%)	Omeprazole	2	0	0	2
	Lansoprazole	1	0	0	1
	Pantoprazole	1	0	0	1
Hormones 4/76 (5.3%)	Estro-progestinics	4	0	2	2
Anti-epileptics 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
Hypo-lipidemic 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%)

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466 **Table 5.** Histological features and direct immunofluorescence panel in the two patients' groups

Histological features	Tot. cohort N (%)	I-SCLE (n=164)	DI-SCLE (n=66)	Observed p- value
Epidermal atrophy	149 (64.8)	105 (64)	44 (66.7)	0.761
Epidermal hyperplasia	35 (15.2)	19 (11.6)	16 (24.2)	0.024*
Keratinocyte necrosis/apoptosis	138 (59.5)	90 (54.9)	48 (72.8)	0.017*
Hyper/orthokeratosis	76 (33)	51 (31.1)	25 (37.9)	0.354
Vacuolar degeneration	206 (89.6)	149 (90.8)	57 (86.4)	0.343
Perivascular lymphocytic infiltrate	225 (97.8)	161 (98.2)	64 (97)	0.627
Periadnexal lymphocytic infiltrate	120 (52.2)	91 (55.5)	29 (43.4)	0.144
Cytoid bodies in the dermis	58 (25.2)	34 (20.7)	24 (36.4)	0.018*
Eosinophils	14 (6)	9 (5.5)	5 (7.6)	0.551
Mucin deposition	138 (60)	114 (69.5)	24 (36.4)	0.000005***
Leukocytoclastic vasculitis	7 (3)	0 (0)	7 (10.6)	0.00013***
Direct immunofluorescence	Tot. cohort N (%)	I-SCLE (n=90) (%)	DI-SCLE (n=43)(%)	p-value
IgG alone	4 (3)	2 (2.2)	2 (4.7)	0.594

IgM alone	7 (5.3)	6 (6.7)	1 (2.3)	0.427
C3c alone	5 (3.7)	3 (3.3)	2 (4.7)	0.658
IgG + C3c	7 (5.3)	3 (3.3)	4 (9.3)	0.212
IgM + C3c	56 (42.1)	47 (52.2)	9 (20.9)	0.00069***
IgG + IgM + C3c	13 (9.8)	9 (10)	4 (9.3)	1.00
* p-value < 0.05; *** p-value < 0.01; Bonferroni adjusted-critical value 0.0045 for t₍₁₁₎ hypothesis.				

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Capsule summary

- Distinguishing drug-induced from idiopathic subacute lupus erythematosus is challenging, as their clinical, histopathological 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, while mucin deposition and positive immunofluorescence are clues to the idiopathic form.