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Analysis of clinical characteristics of drug-induced cutaneous lupus erythematosus in men

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To the editor:

Cutaneous lupus erythematosus (CLE) can be divided into acute (ACLE), subacute (SCLE) and chronic (CCLE). Pathogenesis for CLE includes genetic predisposition, autoimmunity, and drug exposure.¹ Though previous studies have evaluated incidence and clinical characteristics of CLE^{2–4}, none has focused on CLE in men, and in particular, the incidence of drug-induced CLE (DICLE) in men.

This retrospective study describes the clinical characteristics of men diagnosed with CLE and systemic lupus erythematosus (SLE) with cutaneous features at Duke University Medical Center between 2007 and 2017, and specifically compares the patients with DICLE to those with non-DICLE. Clinical characteristics and laboratory test results were obtained by chart review. Statistical analyses were performed with JMP (v13.0, SAS, Cary, NC). Duke University's institutional review board approved this protocol (No. 00084622).

In all, 31 male patients were diagnosed with CLE (Table 1). 9 out of 31 patients (29%) were diagnosed with DICLE based on disappearance of symptoms after discontinuation of offending drugs, including anti-hypertensives and proton-pump inhibitors. The mean age at onset of CLE overall was 43 years (range 8–75 years), but was higher among patients with DICLE compared to non-DICLE patients (62 vs 36 years old, $P<0.0001$). Men with DICLE were more likely to be Caucasian ($P=0.036$) and to have SCLE and bullous CLE ($P=0.020$ and $P=0.022$, respectively). No African-American men in our cohort had DICLE, but

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Conflicts of Interest:

Dr. Anne Marano is a principal investigator for a study for Viela Bio, a phase I trial of VIB7734 in patients with systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), Sjögren's syndrome, systemic sclerosis, polymyositis and dermatomyositis

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comprised the majority (55%) of non-DICLE male patients. The mean drug-to-symptom onset time among DICLE patients was 6.5 weeks (range, 3.8–12.5 weeks). The histopathology in DICLE was less likely than non-DICLE to show interface dermatitis ($P=0.027$). There was no significant difference between the two groups in areas of involvement, systemic features or autoantibody positivity.

There are limitations to our study. Our sample size is small, as CLE occurs less frequently in men. Secondly, the diagnostic criteria of DICLE is not clearly defined. In our cohort, the diagnosis was based on symptomatic improvement after drug withdrawal, potentially underestimating the true incidence of DICLE in men. Lastly, there is heterogeneity in histologic features and autoantibodies tested during the study period.

The incidence of DICLE in our cohort is 29%, which is higher than rates previously reported in both sexes, including an incidence of 12% by Marzano et al.^{3, 4} This may in part due to men having less likelihood of idiopathic autoimmunity than women. In addition, elderly men frequently take anti-hypertensive medications.¹ Our report is consistent with previous studies that showed that, when compared with non-DICLE, DICLE patients had the following features: 1) older age of onset; 2) median drug-to-onset time of approximately 4–8 weeks; and 3) no specific autoantibody pattern associated with DICLE.^{2–4} Moreover, our cohort suggests that interface dermatitis is observed less commonly in DICLE than in non-DICLE. Furthermore, in the southeastern US, the overall CLE incidence is 3–5 folds higher in African-Americans than in Caucasians in both sexes.⁵ Interestingly, African-American men in our cohort only had non-DICLE. In sum, physicians should remain vigilant about DICLE, particularly when elderly Caucasian male patients present with CLE.

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Table 1 –

Comparison of clinical characteristics of male patients with DICLE vs non-DICLE who were seen in the dermatology and rheumatology clinics at the Duke University Medical Center between November 1, 2007 and October 31, 2017

Metric	Full cohort (n=31)	DICLE (n=9)	Non-DICLE (n=22)	P-value
Mean age at onset, y (range)	43 (8–75)	62 (36–75)	36 (8–66)	<0.0001 ^a
Percentage of total		29	71	
Mean time to onset, y (range)		6.5 (3.8–12.5)		
Offending agents, n (%)		Anti-HTNs, 7 (78) ^b PPIs, 2 (22)		
Race/Ethnicity, n (%)				
Caucasian	15 (48)	7 (78)	8 (36)	0.036
African American	12 (39)	0 (0)	12 (55)	0.0047
Hispanic	4 (13)	2 (22)	2 (9)	0.32
Areas of involvement, n (%)				
Sun exposed	7 (23)	2 (22)	5 (23)	0.96
Widespread	9 (29)	2 (22)	7 (32)	0.60
Head and neck	8 (26)	1 (11)	6 (27)	0.38
Upper limbs	5 (16)	2 (22)	4 (18)	0.81
Lower limbs	1 (3)	1 (11)	0 (0)	0.11
Back	1 (3)	1 (11)	0 (0)	0.11
Subtypes, n (%)				
SCLE	14 (45)	7 (78)	7 (32)	0.020
Discoid	13 (42)	0 (0)	13 (59)	0.0025
Tumid	2 (7)	0 (0)	2 (9)	0.32
Bullous	2 (7)	2 (22)	0 (0)	0.022
Systemic symptoms, n (%)				0.15
With systemic symptoms ^c	13 (42)	2 (22)	11 (50)	
Without systemic symptoms	18 (58)	7 (78)	11 (50)	
Histologic features, n (%)	Full cohort (n=21)	DICLE (n=9)	Non-DICLE (n=12)	P-value
Interface dermatitis	8 (38)	1 (11)	7 (58)	0.027
Lichenoid dermatitis	6 (32)	4 (44)	2 (17)	0.16
Spongiotic dermatitis	2 (10)	2 (22)	0 (0)	0.086
Lymphocytic infiltrate	3 (14)	0 (0)	3 (25)	0.11
Subepidermal bullae	2 (10)	2 (22)	0 (0)	0.086

Metric	Full cohort (n=31)	DICLE (n=9)	Non-DICLE (n=22)	P-value
Autoantibody panel	Full cohort # pos/tot (%)	DICLE # pos/tot (%)	Non-DICLE # pos/tot (%)	P-value
ANA+	20/27 (74)	5/7 (71)	15/20 (75)	0.85
Anti-Ro/SS-A+	8/20 (40)	1/5 (20)	7/15 (47)	0.29
Anti-La/SS-B+	2/20 (5)	1/5 (20)	1/15 (7)	0.39
Anti-SM+	5/20 (25)	0/5 (0)	5/15 (33)	0.14
Anti-RNP+	7/21 (33)	0/5 (0)	7/16 (44)	0.07
Anti-dsDNA+	7/20 (35)	1/5 (20)	6/15 (40)	0.42

^aStudent's t-test. All other statistical comparisons were Pearson's chi-square test.

^bAnti-HTNs include: ACE inhibitors – captopril and enalapril (4/7), beta blockers – sotalol and labetalol (2/7), calcium channel blocker – amlodipine (1/7).

^cSystemic symptoms include: nephritis, joint involvement, pericarditis and thrombocytopenia.

Bold face indicates statistical significance.

DICLE, drug-induced cutaneous lupus erythematosus; Anti-HTNs, anti-hypertensives; PPIs, proton-pump inhibitors; SCLE, subacute lupus erythematosus; ANA, antinuclear antibody; Sm, Smith; RNP, ribonucleoprotein; dsDNA, double-strand DNA.