Cutaneous lupus erythematosus in men: a review of 31 patients at Duke University Medical Center from 2007 to 2017

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INTRODUCTION

- Cutaneous lupus erythematosus (CLE) presents with many dermatologic symptoms, with or without systemic features.
- CLE includes acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE).
- CCLE is subdivided into discoid lupus erythematosus (DLE), lupus erythematosus profundus (LEP), chilblain cutaneous lupus (CHLE) and lupus erythematosus tumidus (LET).
- Pathogenesis of CLE includes genetic predisposition, autoimmunity and drug exposure.[1]
- Drug-induction has emerged to be one of the major considerations for CLE pathogenesis in recent years. Drugs known to induce CLE are summarized in Table-1.

Table 1 – Drugs known to induce CLE

Class	Drugs
Anti-hypertensives	HCTZ, Captopril, Lisinopril, Diltiazem, Nifedipine, Acebutolol
Proton pump inhibitors	Lansoprazole, Omeprazole
Anti-fungals	Terbinafine, Griseofulvin
Anti-epileptics	Carbamazepine, Phenytoin
Statins	Pravastatin, Simvastatin
Antibiotics	Amoxicillin/clavulonate, Ciprofloxacin
NSAIDs	Naproxen, Piroxicam
Chemotherapy	Capecitabine, Paclitaxel, Nivolumab, Pembrolizumab, 5-FU
Biologics	Adalimumab, Etanercept, Infliximab, Abatacept, Ustekinumab, Secukinumab

- Though previous studies evaluated incidence and clinical characteristics of CLE, none has focused on CLE in men. [2-4]

METHODS

- To study the clinical characteristics of men diagnosed with CLE at Duke University Medical Center between 2007 and 2017 and compares the clinical features of patients with drug-induced CLE (DICLE) to those with idiopathic or non-DICLE.
- Clinical characteristics, association with drug exposure, histologic and immunologic test results were obtained by chart review. Statistical analysis were performed with JMP (v13.0, SAS). Duke University's institutional review board approved this protocol (No. 00084622).

RESULTS

Table 2 – Comparison of clinical characteristics of male patients with DICLE vs. non-DICLE diagnosed at Duke University Medical Center

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
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

[a]Student's t-test. All other statistical comparisons were Pearson's chi-square test.
[b]Anti-HTNs include: ACE inhibitors – captopril and enalapril (4/7), beta blockers – sotalol and labetalol (2/7), calcium channel blocker – amlodipine (1/7).
[c]Systemic symptoms include: nephritis, joint involvement, pericarditis and thrombocytopenia.
Bold face indicates statistical significance.

- 9 out of 31 patients (29%) were diagnosed with DICLE based on disappearance of symptoms after discontinuation of offending drugs.
- Mean age at onset of CLE overall was 43 years (range 8-75 years) - higher in DICLE vs non-DICLE patients (62 vs 36 YO, *P*<0.0001).
- Men with DICLE were more likely to be Caucasian, to have SCLE, DLE and bullous CLE but less likely to show interface dermatitis on histology (*P*<0.05).
- Mean drug-to-symptom onset time among DICLE patients was 6.5 weeks (range, 3.8-12.5 weeks).
- There was no significant difference between the two groups in areas of involvement, systemic features or autoantibody positivity.

DISCUSSIONS

- There are limitations to our study:

1) Our sample size is small, as CLE occurs less frequently in men.
2) The diagnostic criteria of DICLE is not clearly defined, potentially underestimating the true incidence of DICLE in men.
3) 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 rather previously reported in both sexes:

1) Marzano et al. reported an DICLE incidence rate of 12% for male and female.[3]
2) Laurinaviciene et al. also reported a similar rate of 20% for DICLE with a female:male ratio of 9:1.[4]

- The high incidence of DICLE in men may be due to:

1) Men having less likelihood of idiopathic autoimmunity than women.
2) Men are more frequently on anti-hypertensive medications, which are highly associated with DICLE.[1] In our cohort, 7 out of 9 DICLE patients were on anti-HTN medications.

- Our report is consistent with previous studies that showed that when compared with non-DICLE patients, DICLE patients had the following features:

1) Older age of onset;
2) Median drug-to-onset time is approximately 4-8 weeks;
3) No specific associated autoantibody pattern.[2-4]

- The overall CLE incidence is 3-5 folds higher in African-Americans than in Caucasians in both sexes as indicated in a report by Drenkard et al in the Southeastern US.[5] Interestingly, African-American men in our cohort only had non-DICLE whereas Caucasian men more commonly presented with DICLE.
- Further study to better define the association between drugs and CLE in men is warranted.
- Physicians should remain vigilant about DICLE, particularly when eldely Caucasian male patients present with CLE.

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Abstract

Importance & Objective: Cutaneous lupus erythematosus (CLE) is a heterogenous disease with varying clinical features. Though previous studies have evaluated CLE, none focused on CLE in men in the US. The objective of this study was to evaluate the incidence and clinical characteristics of CLE in men evaluated at Duke University Medical Center from 2007 to 2017.

Design, **Setting & Participants**: This study reviewed medical records of men diagnosed with CLE at Duke University Medical Center between 2007 and 2017. Clinical characteristics, association with drug exposure, histologic and immunologic test results were obtained by chart review.

Main Outcomes and Measures: Participant demographics, clinical, histologic and immunologic findings were recorded.

Results: In all, 31 male patients were diagnosed with CLE and 9 out of 31 (29%) were drug-induced CLE (DICLE) based on disappearance of lupus-like symptoms after discontinuation of offending drugs, including anti-hypertensives (77.8%) and proton-pump inhibitors (22.2%). The mean age at onset was 62 years (range, 36-75 years) for DICLE, compared to 43 years (8-75) for all-comers. Mean time-to-symptom-onset was 6.5 weeks (range, 3.8-12.5 weeks). Men with DICLE were more likely to be older, be white and less likely to be black (P=0.000046, P=0.036 and P=0.0047, respectively). There was no significant difference in areas of involvement, systemic features or autoantibody positivity. Additionally, DICLE in men is more likely to be SCLE and bullous CLE (P=0.020 and P=0.022, respectively) but less likely to be DLE (P=0.0025) or show interface dermatitis on histology (P=0.027).

Conclusion and Relevance: CLE in men is more likely to be drug-induced than previous reported in all patients. In addition, we found that DICLE occurs more frequently in Caucasian men. Further study to better define the association between drugs and CLE in men is warranted and physicians should remain vigilant about DICLE when older, white male patients present with lupus-like symptoms.

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