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Worsening skin damage in patients with cutaneous lupus erythematosus may predict development of systemic lupus erythematosus

To the Editor: Up to 20% of patients with cutaneous lupus erythematosus (CLE) will develop systemic lupus erythematosus (SLE).[1,2] Prior studies have compared patient characteristics and clinical findings at baseline to identify risk factors for developing SLE.[2-4] However, variables that change over time, such as skin disease severity, have not been studied. Our study objective was to identify variable risk factors that predispose patients with CLE to develop SLE.

We performed a retrospective cohort study of patients with CLE seen in outpatient dermatology clinics of the University of Texas Southwestern Medical Center and Parkland Health and Hospital System between December 2008 and December 2019. Exclusion criteria included SLE diagnosis at initial visit, coexisting autoimmune disease, and less than 6 months of follow-up. Patient demographics, Cutaneous Lupus Activity and Severity Index (CLASI) scores, Physician Global Assessment (PGA) scores, and American College of Rheumatology (ACR) SLE diagnostic criteria were collected. Baseline characteristics were compared using Fisher's exact test or Wilcoxon rank sum test between patients with CLE only and patients who progressed from CLE to SLE. Longitudinally, PGA scores and SLE diagnostic criteria at each 6-month interval from baseline to year 3 and each 12-month interval afterward were compared using Wilcoxon rank sum tests or *t* tests. To compare CLASI activity and damage trends over time, the average change scores of CLASI activity and damage or the mean of differences between scores from baseline to each follow-up visit[5] was calculated and analyzed via Fisher's exact test.

Of the 69 patients meeting all criteria, 57 (82.6%) remained with CLE (CLE only), and 12 (17.4%) progressed to SLE (CLE to SLE). At baseline, CLE-to-SLE patients had greater ACR SLE diagnostic criteria, immunologic disorders more frequently, worse PGA overall skin scores, and more generalized DLE than patients with CLE (Table I). Longitudinally, more CLE-to-SLE patients (41.7%) showed worsened skin damage than patients with CLE only (15.8%) ($P = .04$), based on average change scores for CLASI damage (Fig 1). CLE-to-SLE patients had worse PGA overall skin scores at month 6 and year 3 ($P = .01$), more ACR SLE criteria ($P < .05$), more immunologic disorder ($P = .01$), and higher frequency of taking prednisone 10 mg/d or more ($P = .01$). No statistical difference existed for CLASI activity average change scores between groups.

We found that more CLE-to-SLE patients showed worsened CLASI damage scores over time than patients with CLE only. Skin damage can accumulate from prior episodes of high skin disease activity. Although CLE-to-SLE patients did not more frequently show worsening disease activity trends than patients with CLE only, many CLE-to-SLE patients had waxing and waning skin activity courses that likely contributed to their higher skin damage scores. Although we suspect that CLE flares may be an indicator of SLE progression, the lack of a common definition of a CLE flare prevented us from measuring this. Small patient sample size, treatment differences, and limited follow-up duration were additional study limitations. Nonetheless, we have shown that information from baseline and follow-up visits can comprehensively identify risk factors in CLE-to-SLE patients. Earlier

Table I. Initial visit demographics and clinical features of patients with CLE only and patients who progress from CLE to SLE

Patient characteristics	CLE only (n = 57)	CLE to SLE (n = 12)	*P* value*
Sex, n (%)			
Male	12 (18.1)	3 (27.3)	.72
Female	45 (81.9)	9 (72.7)	
Age, y, median (IQR)	45.4 (38-57)	43.7 (28.6-53.4)	.20
Race, n (%)			
White	27 (47.4)	2 (16.7)	.07
African American	24 (42.1)	6 (50.0)	
Hispanic	3 (5.3)	3 (25.0)	
Asian	3 (5.3)	1 (8.3)	
Smoking status (current/ever), n (%)†	26 (54.6)	5 (40)	.32
Predominant CLE subtype, n (%)‡			
SCLE	9 (16.4)	2 (16.7)	>.99
CCLE	48 (83.6)	9 (75.0)	
DLE subtype, n (%)			
Localized	27 (78.6)	2 (33.3)	.03
Generalized	9 (21.4)	5 (66.7)	
Follow-up duration, y, median (IQR)	2.6 (1.3-4.8)	3.7 (3.3-4.6)	.21
Number of ACR SLE criteria, n (%)	2 (1-3)	3 (2.5-3)	.004
Individual ACR SLE criteria, n (%)§			
Immunologic disorder	3 (5.1)	4 (33.3)	.02
CLASI scores, median (IQR)			
CLASI activity	3 (2-7)	6 (3.5-14.5)	.07
CLASI damage	2 (0-8)	5 (2.5-10)	.26
Physician overall skin score, median (IQR)‖	8 (7-9)	7 (5.5-7)	.01
Physician skin activity score, median (IQR)‖	8 (7-9)	7 (5.5-8.5)	.07

ACR, American College of Rheumatology; *CLE*, cutaneous lupus erythematosus; *CCLE*, chronic cutaneous lupus erythematosus; *CLASI*, Cutaneous Lupus Erythematosus Disease Area and Severity Index; *DLE*, discoid lupus erythematosus; *IQR*, interquartile range; *SCLE*, subacute cutaneous lupus erythematosus; *SLE*, systemic lupus erythematosus.

**P* value was calculated by Fisher's exact test and/or Wilcoxon rank sum test.

†Data are missing from 10 patients from the CLE-only group.

‡One CLE-to-SLE patient has acute CLE as the predominant CLE subtype.

§Other individual ACR criteria at baseline were not significantly different between the 2 groups.

‖Data are missing from 1 patient from the CLE-only group.

detection of patients at risk for progression may reduce the development of SLE and associated morbidity.

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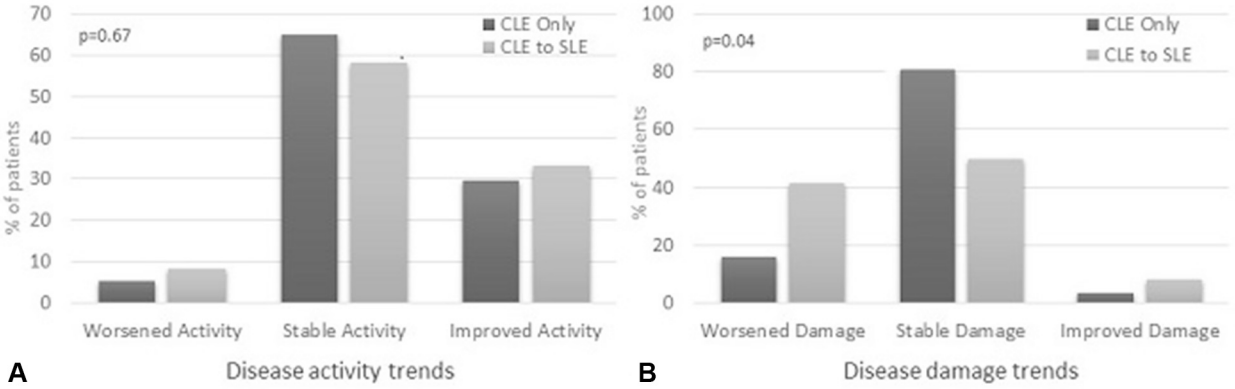

Fig 1. Frequencies of the CLE-only and CLE-to-SLE patients with worsened, stable, or improved disease activity or damage over time. Percentages of those with (**A**) worsened, stable, or improved disease activity or (**B**) damage trends were calculated for patients with CLE only and those with CLE that progressed to SLE. To assess disease activity or damage trends over time, average change scores for CLASI activity and damage were calculated as the mean difference between each patient's follow-up visit scores and baseline visit scores. An average change score of -3 or less indicates improvement, a score of -3 to 3 indicates stability, and a score of 3 or greater indicates worsening of disease activity or damage. *P* values were calculated by Fisher's exact test. *CLE*, Cutaneous lupus erythematosus; *CLASI*, Cutaneous Lupus Erythematosus Disease Area and Severity Index; *SLE*, systemic lupus erythematosus.

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Management of immune checkpoint inhibitor–induced bullous pemphigoid

To the Editor: Management of immune checkpoint inhibitor (ICI)–mediated bullous pemphigoid (BP) is challenging because high doses of systemic corticosteroids, a first-line therapy for classic BP, may jeopardize immunotherapy.[1-3]

We reviewed the records of patients who received ICI and developed BP from January 1, 2017, through October 30, 2019. BP diagnosis was based on clinical, histologic, and immunologic criteria. At baseline, 88.2% (median, 56 UA/mL) and 67.4% (median, 38 UA/mL) of patients had positive results on BP180 and BP230 enzyme-linked immunosorbent assays, respectively. We recorded clinical data, therapeutic intervention, and outcome. BP and pruritus severities were classified using the Common Terminology Criteria for Adverse Events (Fig 1). Thirteen individuals were identified (Table I). The average time from BP onset to diagnosis was 20.6 days. One patient was treated with potent topical steroids, and 12 of 13 individuals were treated with low-dose (0.3-0.5 mg/kg/d; range, 15-40 mg/d) prednisolone. In 11 of 12 treated with systemic steroids, BP was adequately controlled, whereas in 1 of 12 a dose increase to 0.7 mg/kg/d was required (patient 12). The average cumulative prednisone dose and mean time to control of BP were 419.2 mg and 15.8 days,