Not Just Skin Deep: Systemic Disease Involvement in Patients With Cutaneous Lupus

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Cutaneous lupus erythematosus, specifically discoid lupus erythematosus, disproportionately affects those with skin of color and may result in greater dyspigmentation and scarring in darker skin types. In this article, we review investigations relevant to cutaneous lupus patients with skin of color at University of Texas Southwestern Medical Center, associations and risk of progression to systemic lupus, and recommendations for monitoring for systemic disease spread. Between 5% and 25% of patients with cutaneous lupus can develop systemic lupus. If they progress to systemic disease, patients often develop mild systemic disease with primarily mucocutaneous and musculoskeletal manifestations. Patients with cutaneous lupus should be followed up closely to monitor for systemic disease involvement. The University of Texas Southwestern Cutaneous Lupus Erythematosus Registry, of which almost two thirds of participants are those with skin of color, is a part of an ongoing effort to better understand the pathophysiologic mechanisms of CLE and to identify prognostic indicators of risk of progression to systemic lupus.

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a photosensitive cutaneous autoimmune disease with three main subtypes: acute, subacute, and chronic. Acute CLE is characterized by the classic "butterfly rash" and can persist for weeks to months (Werth, 2005). Subacute CLE was initially described by Sontheimer et al. (1979) and manifests as either erythematous annular plaques coalescing into polycyclic plaques or as papulosquamous psoriasiform lesions (Sontheimer, 2005). Chronic CLE has the largest number of subtypes, including discoid lupus erythematous (DLE), lupus erythematosus tumidus, Chilblain's lupus, and lupus panniculitis. The most common type of chronic CLE, DLE (Cardinali et al., 2000; Durosaro et al., 2009), is characterized by erythematous to violaceous scaly papules and plaques in a photosensitive distribution that later develop peripheral hyperpigmentation central atrophy, scarring, and hypopigmentation (Tebbe and Orfanos, 1997). These pigmentary changes can be especially pronounced in patients with skin of color.

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Abbreviations: ANA, anti-nuclear antibody; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; OR, odds ratio; SLE, systemic lupus erythematosus

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THE CLE EXPERIENCE AT UNIVERSITY OF TEXAS SOUTHWESTERN

The University of Texas Southwestern Medical Center's Cutaneous Lupus Erythematosus Registry was established in 2009 with a stated goal of prospectively following CLE patients over time to characterize CLE disease course, identify risk factors for progression to systemic lupus erythematosus (SLE), improve how clinicians diagnose and treat CLE, and predict their prognoses. Participants in the CLE Registry are recruited from outpatient dermatology clinics at University of Texas Southwestern Medical Center and Parkland Memorial Hospital. Almost two thirds of the participants in the registry are those with skin of color, and the most common subtype of CLE represented is chronic CLE. More specifically, two thirds of the registry is composed of participants diagnosed with DLE. About half of the participants meet American College of Rheumatology criteria (Tan et al., 1982) for SLE (Table 1).

Studies investigating quality of life-specific measures in CLE indicate that CLE can have profound effects on quality of life, especially in patients with skin of color (Vasquez et al., 2013). In a multicenter cross-sectional study at University of Texas Southwestern and University of Pennsylvania with inclusion of substantial numbers of patients with skin of color, CLE had a negative effect on quality of life. Female sex, low socioeconomic status, systemic disease, and worse skin disease activity were associated with poor quality of life (Vasquez et al., 2013). In a study of 223 CLE patients at the University of Pennsylvania, African Americans initially presented with greater measures of disease damage than white patients and had higher measures of disease damage at follow-up (Verma et al., 2014).

PROGRESSION OF CLE TO SLE

Although CLE can present in the setting of SLE, it can also occur independently of internal organ involvement (Durosaro et al., 2009). A European database analysis of 1,002 CLE patients showed that 40% of patients with CLE met criteria for SLE, with the most common criteria being a positive test result for anti-nuclear antibody (ANA) and mucocutaneous manifestations, such as photosensitivity and DLE

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Table 1. University of Texas Southwestern CLE Registry participant demographic and clinical characteristics (N = 244)

Characteristic	n	%
Race/ethnicity		
African American/African	116	48
White	88	36
Hispanic	21	9
Asian	9	4
Other	10	4
Sex		
Female	204	84
Male	40	16
Predominant CLE subtype		
CCLE[1]	190	78
SCLE	35	14
ACLE	19	8
Concomitant SLE diagnosis[2]		
Yes	120	49
No	124	51
Number of SLE criteria, mean and SD[2]	4	2.3
SLE criteria[2]		
Photosensitivity	179	73
Discoid rash	175	72
Positive ANA	158	65
Immunologic disorder	90	37
Hematologic disorder	89	36
Arthritis	75	31
Malar rash	65	27
Oral ulcers	64	26
Renal disorder	38	16
Serositis	23	9
Neurologic disorder	3	1

Abbreviations: ACLE, acute cutaneous lupus erythematosus; ANA, anti-nuclear antibody; CCLE, chronic cutaneous lupus erythematosus; CLE, cutaneous lupus erythematosus; SD, standard deviation; SLE, systemic lupus erythematosus.

[1]DLE is the predominant CCLE subtype, accounting for 87% of the CCLE group (165 participants with DLE). Other CCLE subtypes include lupus erythematosus tumidus, Chilblain's lupus, bullous SLE, and lupus panniculitis.

[2]Information refers to data collected at initial visit.

(Biazar et al., 2013). The incidence of CLE is similar to that of SLE, which both have an incidence of approximately 3 per 100,000 (Durosaro et al., 2009).

In 1872, Kaposi was the first to identify progression of DLE to SLE. Subsequent studies investigating this disease progression estimated the incidence to be between 5% and 10% (Millard and Rowell, 1979; Healy et al., 1995). The highest risk of developing SLE appears to be within the first year of diagnosis (Gronhagen et al., 2011), but it has been reported to occur up to 15 years later (Callen, 1985). A recent population-based study from Sweden indicated that progression to SLE can occur in as many as 18% of patients with CLE (Gronhagen et al., 2011). In that study, patients with DLE had a 9.8% probability of being diagnosed with SLE within the first year of diagnosis of CLE, which increased to 16.7% after 3 years. The risk of progression within 3 years of diagnosis was greater in women than men (20.7% vs. 10.4%). In a study of 156 CLE patients in Rochester, MN, 12% of patients developed SLE. The mean time to progression was 8.2 years, and the cumulative incidence of SLE was 5% at 5 years and 23% at 25 years (Durosaro et al., 2009).

In addition, children with DLE can develop SLE. In a retrospective review of 40 pediatric patients with discoid lupus, 26% were later diagnosed with SLE, all within 3 years. The average age at progression to SLE was 11 years. However, those who progressed generally had mild disease, with 89% having disease limited to abnormal laboratory test results and mucocutaneous involvement (Arkin et al., 2015).

To further define disease progression to SLE in CLE patients, researchers at the University of Pennsylvania prospectively followed 77 patients with CLE to assess disease severity and determine which new SLE criteria were met. Of these, 17% developed SLE, with a mean time to diagnosis of SLE of 8.03 years. Most CLE patients who progressed to SLE had mild systemic disease and gained mucocutaneous or immunologic criteria or developed inflammatory arthritis (Wieczorek et al., 2014).

Multiple risk factors have been identified as predictors of systemic spread in CLE (Chong et al., 2012). These include clinical findings such as discoid lesions below the head and neck (generalized DLE) (Callen, 1982; Callen, 1985; Cardinali et al., 2000; Healy et al., 1995; Ng et al., 2000; Scott and Rees, 1959; Vera-Recabarren et al., 2010), periungual telangiectasias, and arthritis. The association between periungual telangiectasias in CLE patients with SLE compared with CLE patients without SLE was first shown when Callen et al. (1982) noted that 76% of SLE patients with DLE showed periungual telangiectasias, whereas 0% of those with DLE but not SLE had them (Callen, 1982). A later study in an Italian cohort comparing 19 DLE patients with SLE versus 166 DLE patients without SLE showed similar results; nailfold abnormalities were present in 76% of 19 patients with DLE and SLE and in no patients with skin-limited disease (Cardinali et al., 2000). Laboratory abnormalities, including high titer ANAs, hematologic abnormalities (leukopenia, anemia), and persistently elevated erythrocyte sedimentation rate, have also been identified as risk factors for systemic spread in DLE (Callen, 1982; Healy et al., 1995; Millard and Rowell, 1979).

There are limited data available on how to delay the onset of SLE in CLE patients. Some evidence exists that prednisone and antimalarials may slow progression. In a retrospective analysis of 130 United States military personnel who developed SLE, the 26 patients who were treated with hydroxychloroquine before SLE diagnosis had a longer duration from first symptom to SLE diagnosis (1.08 vs. 0.29 years) than those who did not receive hydroxychloroquine (James et al., 2007). They also showed lower autoantibody levels over time. However, randomized controlled trials need to be designed to definitively determine whether these medications are effective in preventing or slowing disease progression.

DISCOID LESIONS AS A BENIGN PROGNOSTIC INDICATOR

Discoid lesions have been postulated to portend a benign prognosis in SLE patients. This is based on two studies showing low rates of renal disease in patients with DLE

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