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Cross-Sectional Characteristics of Pediatric-Onset Discoid Lupus Erythematosus: Results of a Multicenter, Retrospective Cohort Study

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Graphical Abstract

Cross-Sectional Characteristics of Pediatric Discoid Lupus Erythematosus

Pediatric discoid lupus erythematosus (DLE) may be associated with systemic lupus (SLE).

In this study, most children with new-onset DLE did not have SLE. Concurrent SLE was highest in female adolescents with generalized DLE, who had clinically aggressive disease.

DLE diagnosis in adolescents should prompt thorough evaluation for SLE.

DLE + SLE Clinical Phenotype

Neurologic disorder
Malar rash Photosensitivity
Generalized DLE
Oral/nasal ulceration
Pleuritis
Pericarditis
Renal disorder
Immunologic/serologic abnormalities
Non-erosive arthritis

DLE patients 7 months

DLE+SLE patients 2 months

Median delay in DLE diagnosis

Median age at rash onset
Median age at DLE diagnosis

0 years   5 years   10 years   15 years   20 years

Stratified cohort of patients with DLE diagnosis at baseline visit

Keywords

pediatric; discoid lupus erythematosus; systemic lupus erythematosus; pediatric rheumatology; pediatric dermatology

Introduction:

Discoid lupus erythematosus (DLE) can cause permanent scarring in cosmetically sensitive areas such as the face and scalp. DLE is the most prevalent cutaneous lupus erythematosus subtype, occurring in up to 80% of affected adults.[1] Untreated DLE causes disfigurement, occupational disability, emotional stress, and lower health related quality of life in adults.[2] Although adults with DLE have a 25% cumulative risk of systemic lupus erythematosus (SLE) over 25 years, most have mild systemic disease.[3]

Pediatric DLE is rare with <3% of cases reported before age 10 years.[4, 5] Pediatric-onset SLE differs from adult-onset SLE, with a more aggressive course, more frequent end-organ damage at presentation, increased requirement for immunosuppression, and two-fold increased mortality risk.[6–9] Delayed diagnosis, late treatment initiation, and poor medication adherence have been associated with increased disease severity and worse health outcomes[8,9] Recent work by our group demonstrated that pediatric dermatologists and rheumatologists do not agree on the baseline risk factors for SLE in pediatric patients with DLE, and that screening approaches to evaluate for systemic disease differ by practice specialty.[10] We found general agreement on baseline labs to screen for SLE but significant diversity in perceived risk factors for systemic disease, with the top 5 most commonly selected high-risk features including the presence of other autoantibodies (besides ANA), arthritis, nephritis, family history of SLE, and serositis. No other baseline risk factors were

agreed upon as high-risk baseline features for SLE, including those previously elucidated in adults, underscoring a critical practice gap in pediatric DLE.

To address this lack of consensus, our group conducted a multicenter, retrospective cohort study of pediatric patients with DLE who were regularly followed by pediatric dermatologists and/or rheumatologists in North America. The primary aim of this project was to characterize clinical outcomes in pediatric DLE, facilitating future development of a consensus treatment plan to optimize management for children with this disease. This manuscript presents cross-sectional characteristics and clinical phenotypes at presentation of all pediatric patients with DLE to better characterize this uncommon pediatric population whose clinical course may differ from adults.

Materials and Methods:

Study Population

This retrospective observational cohort study was conducted at 17 clinical sites and was approved by each site's Institutional Review Board (IRB) with the University of Wisconsin as the coordinating center. Site demographics are included in the Supplementary Table I. Electronic medical records from January 1, 1997, to December 31, 2018 were searched using the ICD 9/10 diagnosis codes for discoid lupus (605.4, L93, L93.2). Patients followed by pediatric dermatology, pediatric rheumatology, or both, with age 18 years at diagnosis of DLE were included. Exclusion criteria included insufficient documentation or clinical and/or histopathologic findings inconsistent with DLE.

Manual Validation of DLE

Given the lack of specificity of these ICD-9/10 codes, all charts were manually reviewed to ensure a physician-confirmed diagnosis of DLE. Subjects were included only if: 1) an in-person consult with a pediatric dermatologist was conducted in which the diagnosis of DLE was confirmed; 2) there was documented diagnostic agreement in the medical record between a pediatric dermatologist and rheumatologist; and/or 3) a pediatric dermatologist could confirm the diagnosis based on key exam findings in the documentation. Clinical confirmation, with or without clinical-pathological correlation, was deemed sufficient, as skin biopsy was infrequently performed. After manual validation, most sites excluded more than 50% of patients whose charts were identified by ICD codes (Supplementary Table I).

Data Collection and Covariates

Data were collected and entered in REDCap by each participating site. The baseline visit was defined as the first visit available in the medical record with a confirmed diagnosis of DLE (although in cases with transfer of care, diagnosis could have been made before the baseline visit). Sociodemographic covariates included sex, race, ethnicity, age at the baseline visit, age at rash onset, age at DLE diagnosis, distribution of DLE lesions (single lesion, multiple lesions localized to head/neck, or generalized), past medical history, family history of SLE, and type of physician at the baseline visit (rheumatology or dermatology).

Outcome Variables

Clinical and laboratory variables were extracted from medical records in order to assess whether patients could be classified at their baseline visit as having SLE based on the 1997 American College of Rheumatology (ACR) classification criteria (primary outcome) and 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (secondary outcome). [11,12]

Analysis of Data

At the baseline visit, patients were stratified into pediatric DLE, which was skin limited, without SLE by ACR (pDLE-only, defined as those with ACR classification criteria < 4 at baseline visit) and DLE with SLE by ACR (pDLE+SLE, ACR criteria ≥ 4). The designation of pDLE-only included both patients with skin-limited disease and those with autoantibodies or systemic features who did not meet ACR classification criteria for SLE. Baseline demographic, clinical, and laboratory data were compared using descriptive statistics and univariate analysis using chi-square and Wilcoxon test for categorial and continuous variables, respectively. Statistics are shown for the entire cohort and for pDLE-only and pDLE+SLE strata. Except where otherwise indicated, p-values represent comparisons between pDLE-only and pDLE+SLE patients.

Results:

Cohort Description

Of 1537 patients screened by chart review, 438 patients met inclusion criteria (28%). Using the ACR classification criteria, 276 patients (63%) had pDLE-only and 162 (37%) had pDLE+SLE at the baseline visit. Using the SLICC classification criteria, 257 patients (59%) had pDLE-only and 181 (41%) had pDLE + SLE. There was close agreement in diagnosis of pDLE+SLE using ACR and SLICC criteria, with the SLICC criteria being more sensitive: 3 patients had pDLE+SLE by ACR but not by SLICC criteria, while 22 had pDLE+SLE by SLICC but not by ACR criteria.

Demographics for the cohort are summarized in Table I. Most patients in the cohort were female with a 2.6:1 female-to-male ratio. There was a higher F:M ratio in pDLE+SLE patients by ACR (ratio 4.1:1) compared to pDLE-only patients (2.1:1, p=0.004). The cohort was racially and ethnically diverse, with 35% Black, 22% Hispanic, 20% White, and 9% Asian. Combined race/ethnicity data were collected via a single "select all that apply" question based on self-reporting in the demographics of the medical record. The vast majority of patients were reported in only one race/ethnicity category, including those reported as Hispanic ethnicity with no additional race information. Race/ethnicity could not be ascertained from the medical record in 15% of patients. Black and Asian patients were more likely than White and Hispanic patients to present with pDLE+SLE: 63 out of 151 (42%) Black patients and 23/40 (58%) Asian patients in the cohort were diagnosed with SLE at the baseline visit compared to 20/87 (23%) White and 26/95 (27%) Hispanic patients (p<0.001). Compared to pDLE-only patients, pDLE+SLE patients were older at DLE rash onset (median age 12.9 years versus 8.9 years, p<0.001) with a shorter delay from rash onset to diagnosis of DLE (median delay 2.3 months versus 6.6 months, p<0.001). Among

patients diagnosed with pDLE + SLE, 82% (118/144) were ages 10 years or older compared to 132/257 (51.4%) in the DLE-only group. Among those diagnosed with pDLE + SLE at the baseline visit, ages were relatively uniformly distributed among participants 10–17 years old, with n=41 subjects 10–12 years of age, n=52 13–15 years of age, and n=25 16–18 years of age at diagnosis.

Baseline visits were nearly evenly split between outpatient pediatric dermatology (48%) and pediatric rheumatology (44%) visits, with only 6% of visits occurring during a hospital admission. pDLE-only patients were more likely to have seen a dermatologist at the baseline visit, while pDLE + SLE patients were more likely to have seen a rheumatologist at the baseline visit (p<0.001). Patients with pDLE+SLE were also more likely to have a family history of SLE (23% of pDLE+SLE versus 14% of pDLE, p=0.02). At baseline, 38 (8.7%) patients reported a medical history of autoimmune disease (any of autoimmune hepatitis, autoimmune thyroid, "other" autoimmune, demyelinating disease, celiac disease, and/or inflammatory bowel disease) with no difference between pDLE-only and pDLE+SLE. Similarly, no other comorbid conditions exhibited statistically significant differences between the two groups.

Clinical Characteristics of pDLE

Overall, most patients (73%) presented with localized DLE, defined as disease restricted to the head/neck, as shown in Table I. Those with pDLE+SLE were more likely than those with pDLE-only to have generalized lesions (39% versus 17%, p <0. 001).

Patients frequently presented with other mucocutaneous ACR criteria, such as malar rash (19%), photosensitivity (21%), and mucosal ulcers (17%); these were more common in patients with pDLE+SLE than pDLE-only (p<0.001). As shown in Table II, each individual ACR clinical characteristic was more likely seen in patients with pDLE+SLE than with pDLE-only (all p<0.001). Among SLICC criteria not present in the ACR criteria, biopsy-proven lupus nephritis and non-scarring alopecia were more common in those with pDLE + SLE (both p<0.001, see Supplementary Table II).

Among those with pDLE + SLE, end-organ disease (as defined by the ACR classification criteria at the baseline visit) was common; 41% presented with single-end organ disease (defined as having exactly one of arthritis, renal disease, seizures, psychosis, pleuritis, or pericarditis), and 23% presented with ≧2 organ systems involved. Non-erosive arthritis (47%) and renal disease (27%) were the most common end-organ criteria met by these patients. Only 3% of pDLE + SLE met ACR criteria at the baseline visit by mucocutaneous criteria-only (malar rash, discoid lupus, photosensitivity, nasal/oral ulcerations, but with a negative anti-nuclear antibody (ANA)). The remaining 33% met SLE criteria with mucocutaneous criteria and a positive ANA. Lupus severity scores (SLEDAI) were inconsistently recorded in the medical record, limiting assessment of disease severity.

Laboratory Characteristics of pDLE

Table III presents immunologic, hematologic, and renal laboratory data overall, and for pDLE+SLE and pDLE-only strata. Immunologic evidence of SLE was common in pDLE + SLE, with each of the listed immunologic laboratory findings present in more than

25% of patients, except for anti-beta-2 glycoprotein (13%), and false positive rapid plasma reagin (RPR) test (11%), although not all tests were checked for all patients. Patients with pDLE+SLE were more likely to have high titer ANA levels >1:320, yet 5% of pDLE+SLE patients were ANA-negative.

Discussion

This study details baseline findings of a large multicenter investigation of pediatric DLE (10-fold larger than any previous study of pediatric patients with DLE).[4, 5, 13, 14] Our cohort was female-predominant, with a higher female-to-male ratio in those diagnosed with pDLE+SLE, concordant with findings in both adult DLE and pSLE literature.[1, 15, 16] Like adults, children with DLE were racially/ethnically diverse and most likely to be Black.[17, 18]

The pDLE + SLE cohort was overall older than the pDLE-only group, and 82% of pDLE + SLE subjects were adolescents (ages 10–19, as defined by the World. Health Organization).[19] As expected, those with pDLE +SLE had more laboratory abnormalities reflecting immunologic, hematologic, and renal disease, as well as end-organ dysfunction, as these are criteria for SLE. The ANA-negative status of 5% of those diagnosed with pDLE+SLE at baseline is notably lower than reported rates of 18% of adults with DLE+SLE, although the lack of standardization or information about the specific ANA assays used diminishes the potential significance of this observation.[20] This finding has added relevance following the derivation and utilization of the 2019 EULAR SLE criteria, which requires a positive ANA for SLE classification, as a negative ANA would exclude some patients from participation in SLE clinical trials.[21] Finally, while generalized DLE was more common in patients with pDLE + SLE, as has been described for adults,[17] 17% of patients with pDLE-only presented with generalized disease. Future investigation will elucidate whether these patients are at higher risk for eventual diagnosis of SLE than those with localized disease.

Children with SLE diagnosis at the baseline visit had a shorter time from rash onset to DLE diagnosis relative to pDLE-only. This could be due to systemic complaints or a surrogate marker for other factors, including socioeconomics and/or race.[22] Because DLE is a scarring process and earlier treatment reduces permanent disease damage, this represents a critical area for improvement. Even a wait time of months may permanently scar a child in cosmetically sensitive areas at a time when body image and peer victimization may be significant concerns.

SLE is often thought of as an adolescent-onset disease, with greater disease activity and immunologic disease in post-pubertal patients when compared with younger children.[23] This age distribution may be influenced by the development of sex hormones.[24,25] However, SLE has been reported in children of all ages, with younger patients at higher risk for familial forms of lupus, including those associated with complement deficiency.[26] For this reason, younger children with DLE may be at risk for evolving systemic disease. Investigation of this cohort will be critical to capture the full spectrum of this disease.

The strengths of this study include the large sample size, collaboration of rheumatologists and dermatologists, and the multicenter approach, including broad North American representation. Significant limitations include the retrospective design, with analyses limited by the quality and completeness of the data in the medical record, and referral bias as all sites were tertiary centers. Disease activity could not be assessed due to the retrospective study design, and it was not possible to definitively ascertain whether SLE onset may have preceded versus coincided with DLE onset in pDLE+SLE cases. ANA titer levels were measured, but assay sensitivities likely varied, and the prozone effect (extremely high titer levels reading out as a negative result) could explain the negative ANA in 5% with SLE. Finally, almost 1/3 of those with pDLE + SLE presented with mucocutaneous criteria with autoantibodies in the absence of end-organ disease. As follow up data was collected only in those with pDLE-only, the disease stability or evolution of this cohort with mild SLE remains unknown.

In this cohort, patients with pDLE + SLE were most likely to be adolescents, with SLE diagnosis solidified by positive serologies and/or the presence of end-organ damage. In adolescence, diagnosis of DLE should prompt thorough screening for SLE including referral to rheumatology and consideration of the following SLE screening labs: complete blood counts with differential, urinalysis, complement levels, erythrocyte sedimentation rate, ANA, hepatic function tests, renal function/electrolytes, dsDNA, Sjögren syndrome (SS)A, SSB, Smith (Sm), ribonucleoprotein (RNP) antibodies, C-reactive protein, urine protein : creatinine ratio, and antiphospholipid antibodies. Continued collaboration between dermatologists and rheumatologists will facilitate better understanding of this disease in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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Table I.

Demographics and Characteristics of pediatric patients with pDLE-only vs pDLE + SLE (defined as meeting 4 ACR classification criteria at the baseline visit). Statistically significant values are bolded and italicized.

	pDLE-only n=276, (63%)	pDLE + SLE n=162, (37%)	Total n=438, (%)	P-value
Female sex	185 (67)	130 (80)	315 (72)	*0.004*
Race/Ethnicity				
American Indian/Alaskan Native	1 (0.4)	1 (0.6)	2 (0.5)	0.70
Asian	17 (6)	23 (14)	40 (9)	*0.005*
Black	88 (32)	63 (39)	151 (35)	0.14
Native Hawaiian or Other Pacific Islander	1 (0.4)	1 (0.6)	2 (0.5)	0.70
White	67 (24)	20 (12)	87 (20)	*0.002*
Hispanic or Latino	69 (25)	26 (16)	95 (22)	*0.03*
Unknown or not reported	38 (14)	29 (18)	67 (15)	0.25
Median Age at Baseline Visit (in years)	10.9	13.7	12.0	*<0.001*
Median Age at DLE Rash Onset (in years)	8.9	12.9	10.6	*<0.001*
Median Age at DLE Diagnosis (in years)	10.1	13.3	11.6	*<0.001*
Specialty Seen for Baseline Visit				
Rheumatology	92 (34)	98 (61)	1 (44)	*<0.001*
Dermatology	177 (64)	34 (21)	211 (48)	
In-patient consultation	2 (0.7)	26 (16)	28 (6)	
Other	4 (2)	4 (2)	8 (2)	
Any family history of SLE	39 (14)	37 (23)	76 (17)	*0.02*
1ˢᵗ degree family history of SLE	11 (4)	8 (5)	19 (4)	0.64
Location of DLE lesions				
Localized (restricted to head/neck only)	222 (81)	95 (59)	317 (73)	*<0.001*
Generalized (both above and below the neck)	47 (17)	63 (39)	110 (25)	
Isolated (single lesion)	5 (2)	4 (2)	9 (2)	

Abbreviations: *pDLE-only* (diagnosis of DLE with <4 1997 ACR classification criteria for SLE at the baseline visit; *pDLE + SLE* (diagnosis of DLE with SLE with 4 1997 ACR classification criteria for SLE at the baseline visit); *DLE* (discoid lupus erythematosus); *SLE* (systemic lupus erythematosus)

Table II.

ACR clinical classification criteria at the baseline visit by disease status. All values were statistically significant.

ACR clinical classification criteria	pDLE n=276, (63%)	pDLE + SLE n=162, (37%)	Total n=438, (%)	P- value
Malar rash	12 (4)	73 (45)	85 (19)	*<0.001*
Photosensitivity	31 (11)	61 (38)	92 (21)	*<0.001*
Oral/nasal ulceration	10 (4)	63 (39)	73 (17)	*<0.001*
Non-erosive arthritis [*]	7 (3)	74 (46)	81 (19)	*<0.001*
Renal disorder [$]	5 (2)	42 (26)	47 (11)	*<0.001*
Seizures [%]	0 (0)	7 (4)	7 (2)	*<0.001*
Psychosis [&]	0 (0)	8 (5)	8 (2)	*<0.001*
Pleuritis [#]	0 (0)	9 (6)	9 (2)	*<0.001*
Pericarditis [@]	0 (0)	10 (6)	10 (2)	*<0.001*
Single-organ involvement [**]	12 (4)	67 (41)	79 (18)	*<0.001*
2-organ involvement [***]	0 (0)	37 (23)	37 (8)	*<0.001*

Abbreviations: *pDLE-only* (diagnosis of DLE with <4 1997 ACR classification criteria for SLE at the baseline visit; *pDLE + SLE* (diagnosis of DLE with SLE with 4 1997 ACR classification criteria for SLE at the baseline visit)

From the 1992 update of 1982 ACR classification criteria for SLE.

[*] Non-erosive arthritis = involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion

[$] Renal disorder = persistent proteinuria > 0.5 g/day or > 3+ protein without quantitation or cellular casts

[%] Seizures in the absence of offending drugs or metabolic derangement

[&] Psychosis in the absence of offending drugs or metabolic derangement

[#] Pleuritis = convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion

[@] Pericarditis = documented by EKG or evidence of pericardial effusion.

[**] Includes 1 of the following: non-erosive arthritis, renal disorder, seizures, psychosis, pleuritis/pericarditis

[***] includes 2 of the organs listed above

Table III.

Laboratory studies at the baseline visit by disease status.

	pDLE n=276, (63%)	pDLE + SLE n=162, (37%)	Total n=438, (%)	P-value
Immunologic studies				
ANA titer				
n	236	160	396	
1:40 or negative	126 (53)	8 (5)	134 (34)	***<0.001***
1:80	24 (10)	8 (5)	32 (8)	
1:160	27 (11)	17 (10)	44 (11)	
1:320	15 (6)	14 (9)	29 (7)	
1:640	12 (5)	35 (22)	47 (12)	
1:1280 or higher	11 (5)	53 (33)	64 (16)	
Positive, no titer	21 (9)	25 (16)	46 (12)	
Anti-dsDNA	21/190 (11)	102/157 (65)	123/347 (35)	***<0.001***
Anti-Smith	10/143 (7)	98/148 (66)	108/291 (37)	***<0.001***
Anti-Cardiolipin	6/78 (8)	63/145 (43)	69/223 (31)	***<0.001***
Lupus anticoagulant	4/63 (6)	30/109 (28)	34/172 (20)	***<0.001***
Anti-U1RNP	15/126 (12)	92/143 (64)	107/269 (40)	***<0.001***
Anti-Ro/SSA	43/186 (23)	71/151 (47)	114/337 (34)	***<0.001***
Anti-La/SSB	13/184 (7)	41/148 (28)	54/332 (16)	***<0.001***
Anti- B2 glycoprotein	5/47 (11)	12/91 (13)	17/138 (12)	0.67
Anti-Histone	1/11 (9)	7/21 (33)	8/32 (25)	0.13
Low C3	7/152 (5)	104/158 (66)	111/310 (36)	***<0.001***
Low C4	19/152 (13)	103/157 (66)	122/309 (40)	***<0.001***
Low CH50	4/48 (8)	29/50 (58)	33/98 (34)	***<0.001***
Elevated ESR	44/146 (30)	111/140 (79)	155/286 (54)	***<0.001***
+Coombs	6/29 (21)	51/90 (57)	57/119 (48)	***<0.001***
False + RPR	2/23 (9)	4/36 (11)	6/59 (10)	0.76
Hematologic Studies				
Leukocytopenia 4,000	17/209 (8)	76/155 (49)	93/364 (26)	***<0.001***
Thrombocytopenia 100,000	3/212 (1)	32/158 (20)	35/370 (10)	***<0.001***
Lymphopenia				***<0.001***
N	230	148	378	
1,000	3 (1)	44 (30)	47 (12)	
1,000 – 1,500	6 (3)	37 (25)	43 (11)	
> 1,500	221 (96)	67 (45)	288 (76)	

Abbreviations: *pDLE-only* (diagnosis of DLE with <4 1997 ACR classification criteria for SLE at the baseline visit; *pDLE + SLE* (diagnosis of DLE with SLE with 4 1997 ACR classification criteria for SLE at the baseline visit); *ANA titer*: anti-nuclear antibody titer; *anti-dsDNA*: anti-double stranded deoxyribonucleic acid; *anti-U1RNP*: ; *Anti-Ro/SSA; Anti=La/SSB; Anti-B2-glycoprotein; Low C3; Low C4; Low CH50; Elevated ESR; +Coombs; False +RPR*