The BWH Lupus Cohort 1970-2011:

Association of Discoid Lupus with other Clinical Manifestations among Patients with Systemic Lupus Erythematosus

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Overview

- Clinical Background
- Background: SLE phenotypic subsets
- SLE associations with Discoid Lupus: BWH Lupus Registry
  - Prognostic implications?
  - Survival analysis
- Future directions

Clinical Background

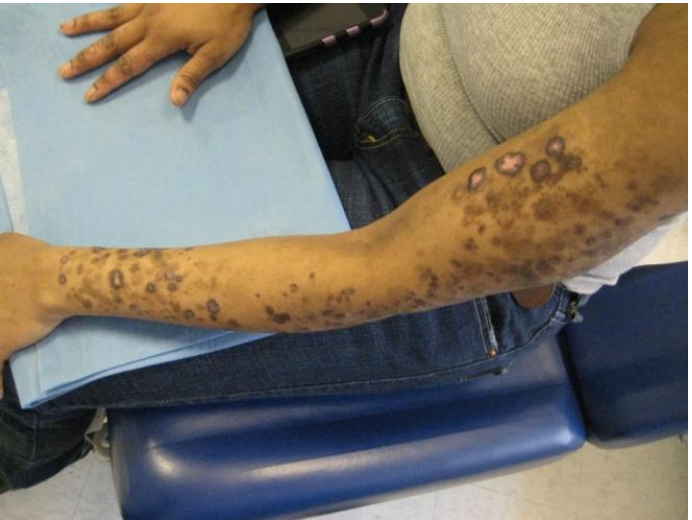
Introduction / Clinical

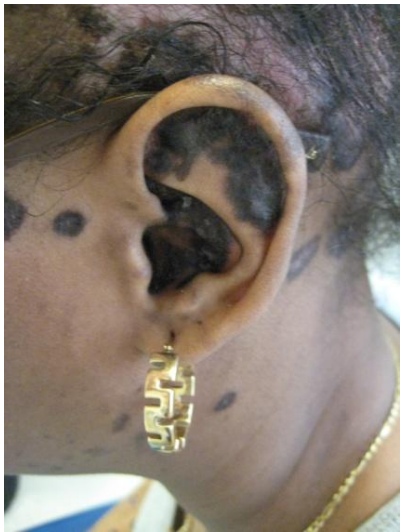
- SLE is a very heterogeneous disease
- Subtypes / clusters of disease thought to exist based on manifestations and serologies
- Significance:
  - prognostication
  - drives treatment decisions & monitoring recommendations
  - offers phenotypes for study: mechanistic, trials

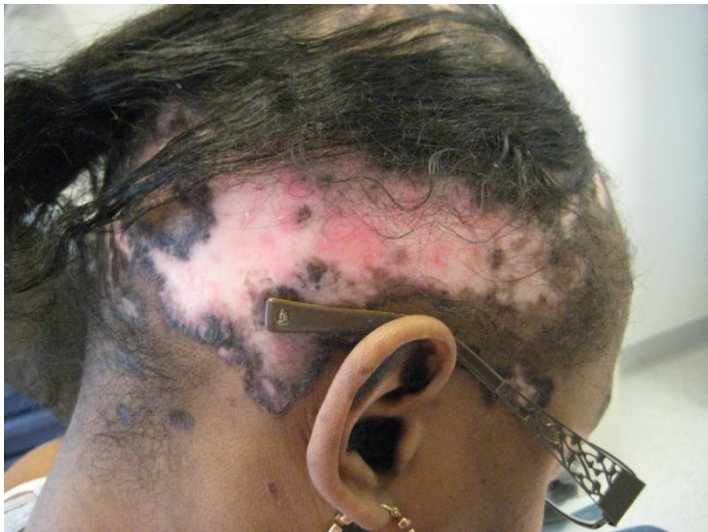
Introduction / Clinical (cont.)

- Chronic Cutaneous Lupus / ‘Discoid’

  – Potentially disfiguring, scarring skin disease
  – Case series, observational studies (mostly dermatology literature) suggest a better prognosis for SLE patients with discoid lupus than those without
  – Important prognostic information to patients





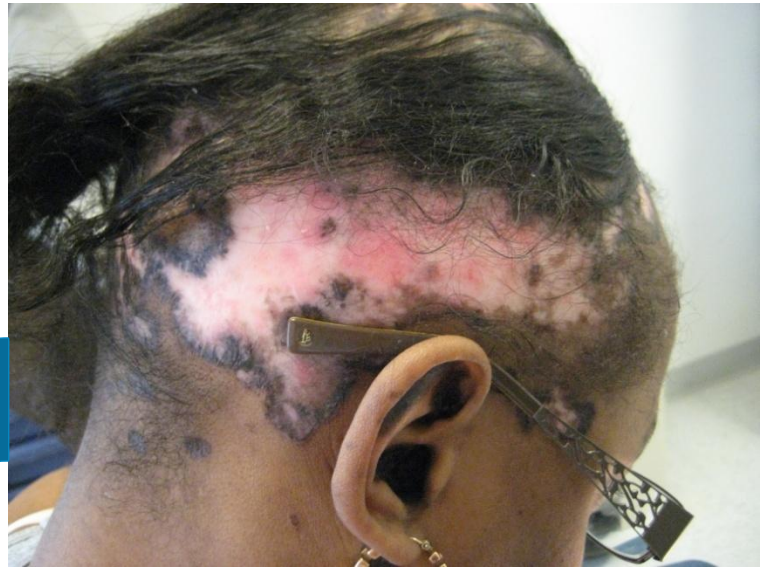


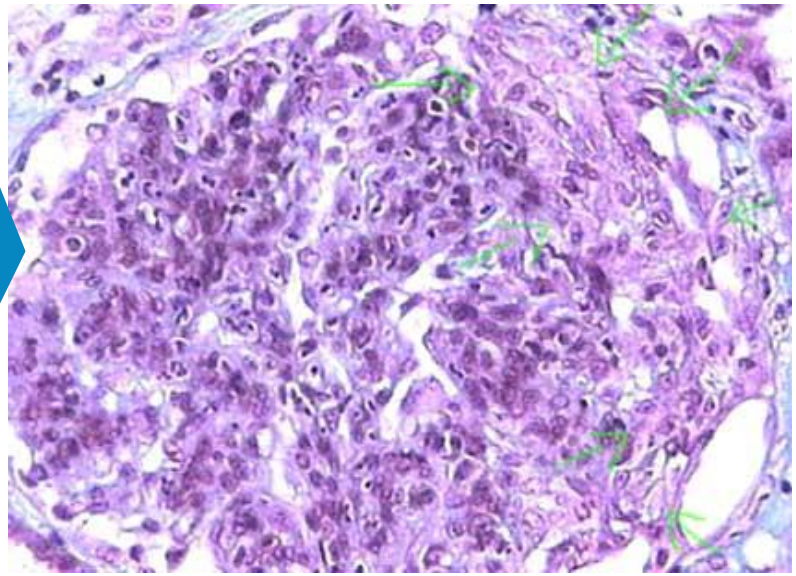
Does the presence of discoid lupus offer prognostic information for the SLE patient?

- Lupus Nephritis*
  - –Clinically evident renal disease present in 28-50% of pts with SLE
  - –10-30 % of proliferative lupus nephritis progress to end-stage renal disease

- Can we give any prognostic information to the SLE patient with discoid features?

?





* Kasitanon N, Magder LS, Petri M
Predictors of survival in systemic lupus erythematosus.
Medicine (Baltimore). 2006;85(3):147.

December 2011 1413 Volume 10 • Issue 12

ORIGINAL ARTICLES
Journal of Drugs in Dermatology

Is Chronic Cutaneous Discoid Lupus Protective Against Severe Renal Disease in Patients With Systemic Lupus Erythematosus?

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- Observational study
- N=20, pts with SLE duration 5-10 years (retrospective data)
- Followed for 3 years for development nephritis (prospectively followed)
- 1 year incidence rate nephritis reported in past at 10%*
- 31-65 % of SLE patients developing some form of nephritis*
- 0 patients developed nephritis
- ? Clinic / referral bias

*Skovron ML, Petri M. Frequency of renal manifestations in the Johns Hopkins SLE Cohort. Arthitis Rheum. 1997; 40(9): S220

Phenotypic Subsets: Background

Summary (and Limitations) of Past Studies

- Clusters of SLE phenotypes identified by serologies→ not mutually exclusive or highly predictive

Is Antibody Clustering Predictive of Clinical Subsets and Damage in Systemic Lupus Erythematosus?

C. H. To and M. Petri

ARTHRITIS & RHEUMATISM
Vol. 52, No. 12, December 2005, pp 4003–4010

- Clusters of SLE phenotypes identified by manifestations→ not mutually exclusive or highly predictive

- Phenotypes may be associated with survival (Chinese population):

Prognostically distinct clinical patterns of systemic lupus erythematosus identified by cluster analysis

CH To[1], CC Mok[1], SSK Tang[2], SKY Ying[2], RWS Wong[3] and CS Lau[4]

Lupus (2009) 18, 1267–1275

- Clinical observations: patients with SLE and discoid lupus have seemingly inverse relationship with lupus nephritis

- Recent study in the PROFILE cohort; SLE patients with discoid →
  - Less likely to have: arthritis, ESRD, anti-dsDNA, APLA; ? No assoc with nephritis/GFR/proteinuria
    - Specific DLE subset not confirmed
    - Medication effects not assessed

Association of Discoid Lupus with Clinical Manifestations and Damage Accrual in PROFILE: A Multiethnic Lupus Cohort

Yesenia Santiago-Casas, MD[1]; Luis M. Vilá, MD[1]; Gerald McGwin, Jr., PhD[2,3]; Ryan S. Cantor, MSPH[2],Michelle Petri, MD, MPH[4]; Rosalind Ramsey-Goldman, MD, DrPH[5]; John D. Reveille, MD[6]; Robert P. Kimberly, MD[7], Graciela S. Alarcón, MD, MPH[7]; Elizabeth E. Brown, PhD,

Arthritis Care and Research. 2011 Dec 20.

Autoantibody and Clinical Profiles in Patients With Discoid Lupus and Borderline Systemic Lupus

- Examined patients with DLE, DLE/'borderline' SLE, DLE/SLE

- Cluster analysis of clinical manifestations and serologies:
  - DLE and borderline SLE/DLE cluster together
  - DLE/SLE

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Lin-chiang Tseng, BS
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ARCH DERMATOL/VOL 148 (NO. 5), MAY 2012

SLE Associations with Discoid Lupus: The BWH Lupus registry

Study Design

- BWH Lupus Registry Data
  - contains data on patients from 1970 – present
  - >5000 pts screened, 1700+ with validated SLE in registry

- Inclusion criteria:
  - ‘Definite’ SLE expert review of chart / criteria
  - Fulfillment of 4/11 ACR 1997 classification criteria
  - >2 visits and > 3 months of follow-up
  - Documented year of diagnosis

- Data collection from EMR including serologies, medications, clinical labs, confirmed outcomes, clinical manifestations

Confirmation of DLE cases: ('outcome')

- Specific diagnosis of 'discoid' lupus by specialist dermatologist notes
- AND supported by *at least one* of:
  - (1) a clinical description consistent with DLE
    - elements including follicular plugging, dyspigmentation, atrophy, scar formation, scarring-alopecia, telangiectasia, erythema, scale - *with emphasis on chronic scarring changes*
  - (2) histopathologic results consistent with DLE in the medical records
  - (3) photographs in the medical records confirming DLE lesions

Statistical Methods

- Multivariable-adjusted logistic regression analyses to test for associations between DLE and, *individually*, each of the ACR SLE criteria and ESRD among SLE patients
  - **adjusted for:** age at diagnosis, sex, race/ethnicity, disease duration, medication use:
    - steroids (ever/never)
    - hydroxycholorquine (ever/never)
    - immunosuppressives (azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, systemic corticosteroids – ever/never)

- variables with $p \leq 0.05$ considered to be significant
- confounder and potential problematic collinearity in our regression models
  - 'Belsey-Kuh-Welsch' collinearity diagnostics such as tolerance and variance inflation factor review, and principle components
- evaluate for effect modification between race and DLE

n=1043

Table 1. Sociodemographic Features of SLE patients with and without Discoid Lupus.

Feature	SLE without Discoid Lupus n=926 (90%)	SLE with Discoid Lupus n=117 (10%)	p-value*
Female (%)	847 (92)	111 (95)	0.28
Race/Ethnicity (%)			
Caucasian	480 (52)	56 (48)	**0.02**
African American	130 (14)	31 (27)	
Hispanic	41 (4)	6 (5)	
Asian	83 (9)	8 (7)	
Other	10 (1)	1 (1)	
Missing race/ethnicity	182 (19)	15 (12)	0.09
Age at Diagnosis in Years, mean (SD)	32.6 (13.5)	32.0 (12.6)	0.91
SLE Duration in Years, mean (SD)	18.4 (10.6)	18.4 (10.5)	0.90
Number of ACR criteria for SLE, mean (SD)	**5.2 (1.2)**	**5.6 (1.4)**	**<0.01**
Medications	n (%)	n (%)	
Hydroxychloroquine	739 (80)	103 (88)	0.05
Mycophenylate	178 (20)	24 (20)	0.71
Corticosteroids (systemic)	693 (75)	88 (75)	1.00
Methotrexate	101 (11)	18 (15)	0.16
Cyclophosphamide	101 (11)	15 (13)	0.53
Azathioprine	204 (22)	30 (26)	0.41
Rituximab	26 (3)	1 (1)	0.35
Leflunomide	22 (2)	2 (2)	1.00

*Fisher's exact tests for categorical variables (race/ethnicity). Wilcoxon rank sum tests for continuous variables and chi-square tests for medications.

Merola J, et al. In press, JAAD 2013

Discoid lupus with other clinical manifestations in SLE

Table 2. Associations between Discoid Lupus and other ACR Criteria for SLE as well as End-Stage Renal Disease

SLE Manifestation (n=positive finding out of 1043)	SLE without DLE (n=926) n (%)	SLE with DLE (n=117) n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	Adjusted OR** (95% CI)
Anti-Smith	201 (21.7)	45 (38.5)	2.25 (1.50-3.38)	**2.27 (1.50-3.45)**	**2.41 (1.58-3.69)**
Photosensitivity	374 (40.4)	60 (51.3)	1.55 (1.06-2.28)	**1.71 (1.15-2.55)**	**1.63 (1.09-2.44)**
Leukopenia	301 (32.5)	50 (42.7)	1.55 (1.05-2.29)	**1.50 (1.01-2.24)**	**1.55 (1.03-2.32)**
Pleuritis	349 (37.7)	31 (26.5)	0.59 (0.39-0.92)	**0.56 (0.36-0.88)**	**0.56 (0.36-0.87)**
Arthritis	738 (79.7)	79 (67.5)	0.53 (0.35-0.80)	**0.51 (0.33-0.79)**	**0.49 (0.31-0.76)**
Lupus Nephritis	281 (30.3)	38 (32.5)	1.10 (0.73-1.66)	1.09 (0.71-1.68)	1.33 (0.83-2.14)
Pericarditis	112 (12.1)	10 (8.6)	0.68 (0.35-1.34)	0.68 (0.34-1.36)	0.68 (0.34-1.36)
Proteinuria	256 (27.7)	27 (23.1)	0.78 (0.50-1.23)	0.70 (0.43-1.13)	0.77 (0.47-1.27)
Casts	117 (12.6)	9 (7.7)	0.56 (0.28-1.17)	0.53 (0.26-1.09)	0.57 (0.27-1.20)
End-Stage Renal Disease	48 (5.1)	7 (6.0)	1.16 (0.51-2.64)	0.96 (0.41-2.22)	1.24 (0.50-3.05)
Oral ulcers	240 (25.9)	37 (31.6)	1.32 (0.87-2.00)	1.35 (0.88-2.07)	1.32 (0.86-2.03)
Malar Rash	406 (43.8)	46 (39.3)	0.82 (0.56-1.23)	0.86 (0.57-1.30)	0.88 (0.58-1.32)
Seizure	100 (10.8)	14 (12)	1.12 (0.61-2.03)	1.14 (0.62-2.09)	1.20 (0.65-2.21)
Psychosis	16 (1.7)	3 (2.6)	1.50 (0.43-5.21)	1.45 (0.41-5.14)	1.50 (0.42-5.38)
Anemia	181 (19.5)	26 (22.2)	1.17 (0.74-1.87)	1.12 (0.69-1.80)	1.15 (0.71-1.86)
Lymphopenia	340 (36.7)	51 (43.6)	1.33 (0.90-1.96)	1.32 (0.88-1.97)	1.38 (0.91-2.08)
Thrombocytopenia	110 (11.9)	18 (15.4)	1.35 (0.79-2.31)	1.45 (0.83-2.54)	1.54 (0.87-2.71)
Anti-dsDNA	610 (65.9)	83 (70.9)	1.27 (0.83-1.93)	1.25 (0.81-1.93)	1.33 (0.86-2.07)
Antiphospholipid antibodies	225 (24.3)	24 (20.5)	0.80 (0.50-1.29)	0.85 (0.52-1.37)	0.87 (0.54-1.43)

Merola J, et al. In press, JAAD 2013

Associations between Discoid Lupus and SLE criteria/ESRD (SLE patients with DLE vs. those without DLE)

	SLE Manifestation	Adjusted OR (95% CI)
+	Anti-Smith	2.41 (1.58-3.69)*
+	Photosensitivity	1.63 (1.09-2.44)*
+	Leukopenia	1.55 (1.03-2.32)*
-	Pleuritis	0.56 (0.36-0.87)*
-	Arthritis	0.49 (0.31-0.76)*
Ø	Nephritis	1.33 (0.83-2.14)
Ø	Proteinuria	0.77 (0.47-1.27)
Ø	Casts	0.57 (0.27-1.20)
Ø	ESRD	1.24 (0.50-3.05)
Ø	Anti-dsDNA	1.33 (0.86-2.07)

<u>NO</u> significant association between DLE and the following were found:
Pericarditis, oral ulcers, malar rash, seizure, psychosis, anemia, lymphopenia, thrombocytopenia, anti-phospholipid antibodies

Conclusions

- Among SLE patients with DLE:
  - Increased frequency of photosensitivity, leukopenia and anti-Smith antibodies
  - Inverse association of DLE with both pleuritis and arthritis

- We did *not* observe the inverse associations of DLE with anti-dsDNA antibodies, lupus nephritis, or ESRD that have been noted in other studies

- Implications for prognosis among patients with DLE

- ? possibly different underlying pathophysiologies of SLE subtypes

Limitations

- Missing data: BWH Lupus Registry may have incomplete data and some patients seen only for brief time (ie: 'second opinion') → lack of clinical data
    - Excluded if ≤ 2 visits, < 3 months f/u time
- Cross-sectional Lupus Registry -> built into a retrospective cohort
- Associations: cannot temporally relate these clinical features or imply a causal relationship
- Regression models were performed as independent tests
    - possibility of issues surrounding multiple testing
    - future studies may be performed to reproduce our individual findings

Survival DLE-SLE

- **Objective:** To investigate whether there exists a survival difference among SLE patients with DLE vs. those without DLE in an academic lupus center over the past 41 years

- **Inclusion Criteria:**
  - ≥ 4/11 of the 1997 American College of Rheumatology SLE Criteria
  - > 2 visits to our center
  - Diagnosis ≥ January 1, 1970
  - Age ≥ 18
  - Patients followed for ten years, or until death or end of follow-up (April 30, 2011)

  - **Methods:**
    - We employed Kaplan Meier curves with log rank tests and Cox proportional hazards models, adjusted for diagnosis age, race, sex, hydroxychloroquine use and immunosuppressive medication use (azathioprine, mycophenolate, cyclophosphamide), to estimate risks of death.

- N=892

Unpublished data

Results

There was *no* significant association between the presence of discoid lupus (DLE) among SLE patients and 10 year survival in a model adjusted* for hydroxychloroquine exposure, immunosuppressive medication exposure, age at diagnosis, race (White, Black, Hispanic, Asian, other), sex.

Likely underpowered to detect a smaller difference

N=892	Alive	Deceased	
No DLE	710 (90%)	79 (10%)	p=0.86
DLE	94 (91.3)	9 (8.7%)	

	Adjusted* Hazard Ratio for Death within 10 years of Diagnosis (95% CI)
DLE	1.00 (0.50-2.04)

Unpublished data

Future Directions

Future Directions

- Clinical phenotypes differentiated by cytokine profiles
- Cytokine profiles pre- and post- treatment

Thank you

- BWH Lupus Center and the Rheumatology Section for Clinical Sciences
    - Tabatha Norton, Peter Tsao, Jose Gomez-Puerta, Christina Iversen, Uzoma Oranu
- Mentor: Karen Costenbader, MD MPH
- BWH Dermatology:
    - Abrar Qureshi, MD MPH
    - Ruth Ann Vleugels, MD MPH

This study supported in part by:
NIAMS T32AR007530 and P60AR057782