The BWH Lupus Cohort 1970-2011:

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

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Mentor: Karen Costenbader, MD, MPH
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
• 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
Is Chronic Cutaneous Discoid Lupus Protective Against Severe Renal Disease in Patients With Systemic Lupus Erythematosus?

Joseph F. Merola MD, a Caroline A. Chang MD, b Miguel R. Sanchez MD, c Stephen D. Prystowsky MD c

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bTufts Medical Center, Boston, MA
cNew York University School of Medicine, New York, NY

• 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

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. 4003–410

• 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 To¹, CC Mok², SSK Tang², SKY Ying², RWS Wong² and CS Lau¹

  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, MD¹; Luis M. Vila, MD¹; Gerald McGwin, Jr., PhD²; Ryan S. Cantor, MSPH³; Michelle Petri, MD, MPH⁴; Rosalind Ramsey-Goldman, MD, DrPH⁵; John D. Reveille, MD⁶; Robert P. Kimberly, MD⁷; Graciela S. Alarcón, MD, MPH⁸; Elizabeth E. Brown, PhD, Arthritis Care and Research. 2011 Dec 20.
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

Rebecca Vasquez, MD
Lin-chiang Tseng, BS
Sandra Victor, BS
Song Zhang, PhD
Benjamin F. Chong, MD

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)
    - hydroxychloroquine (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
Table 1. Sociodemographic Features of SLE patients with and without Discoid Lupus.

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

*Fisher’s exact tests for categorical variables (race/ethnicity). Wilcoxon rank sum tests for continuous variables and chi-square tests for medications.
Table 2. Associations between Discoid Lupus and other ACR Criteria for SLE as well as End-Stage Renal Disease

<table>
<thead>
<tr>
<th>SLE Manifestation</th>
<th>SLE without DLE (n=926)</th>
<th>SLE with DLE (n=117)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
<th>Adjusted OR** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n-positive finding out of 1043)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Smith</td>
<td>201 (21.7)</td>
<td>45 (38.5)</td>
<td>2.25 (1.50-3.38)</td>
<td>2.27 (1.50-3.45)</td>
<td>2.41 (1.58-3.69)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>374 (40.4)</td>
<td>60 (51.3)</td>
<td>1.55 (1.06-2.28)</td>
<td>1.71 (1.15-2.55)</td>
<td>1.63 (1.09-2.44)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>301 (32.5)</td>
<td>50 (42.7)</td>
<td>1.55 (1.05-2.29)</td>
<td>1.50 (1.01-2.24)</td>
<td>1.55 (1.03-2.32)</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>349 (37.7)</td>
<td>31 (26.5)</td>
<td>0.59 (0.39-0.92)</td>
<td>0.56 (0.36-0.88)</td>
<td>0.56 (0.36-0.87)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>738 (79.7)</td>
<td>79 (67.5)</td>
<td>0.53 (0.35-0.80)</td>
<td>0.51 (0.33-0.79)</td>
<td>0.49 (0.31-0.76)</td>
</tr>
<tr>
<td>Lupus Nephritis</td>
<td>281 (30.3)</td>
<td>38 (32.5)</td>
<td>1.10 (0.73-1.66)</td>
<td>1.09 (0.71-1.68)</td>
<td>1.33 (0.83-2.14)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>112 (12.1)</td>
<td>10 (8.6)</td>
<td>0.68 (0.35-1.34)</td>
<td>0.68 (0.34-1.36)</td>
<td>0.68 (0.34-1.36)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>256 (27.7)</td>
<td>27 (23.1)</td>
<td>0.78 (0.50-1.23)</td>
<td>0.70 (0.43-1.13)</td>
<td>0.77 (0.47-1.27)</td>
</tr>
<tr>
<td>Cysts</td>
<td>117 (12.6)</td>
<td>9 (7.7)</td>
<td>0.56 (0.28-1.17)</td>
<td>0.53 (0.26-1.09)</td>
<td>0.57 (0.27-1.20)</td>
</tr>
<tr>
<td>End-Stage Renal Disease</td>
<td>48 (5.1)</td>
<td>7 (6.0)</td>
<td>1.16 (0.51-2.64)</td>
<td>0.96 (0.41-2.22)</td>
<td>1.24 (0.50-3.05)</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>240 (25.9)</td>
<td>37 (31.6)</td>
<td>1.32 (0.87-2.00)</td>
<td>1.35 (0.88-2.07)</td>
<td>1.32 (0.86-2.03)</td>
</tr>
<tr>
<td>Malar Rash</td>
<td>406 (43.8)</td>
<td>46 (39.3)</td>
<td>0.82 (0.56-1.23)</td>
<td>0.86 (0.57-1.30)</td>
<td>0.88 (0.58-1.32)</td>
</tr>
<tr>
<td>Seizure</td>
<td>100 (10.8)</td>
<td>14 (12)</td>
<td>1.12 (0.61-2.03)</td>
<td>1.14 (0.62-2.09)</td>
<td>1.20 (0.65-2.12)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>16 (1.7)</td>
<td>3 (2.6)</td>
<td>1.50 (0.43-5.21)</td>
<td>1.45 (0.41-5.14)</td>
<td>1.60 (0.42-5.38)</td>
</tr>
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<td>Anemia</td>
<td>181 (19.5)</td>
<td>26 (22.2)</td>
<td>1.17 (0.74-1.87)</td>
<td>1.12 (0.69-1.80)</td>
<td>1.15 (0.71-1.86)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>340 (38.7)</td>
<td>51 (43.6)</td>
<td>1.33 (0.90-1.96)</td>
<td>1.32 (0.88-1.97)</td>
<td>1.38 (0.91-2.08)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>110 (11.9)</td>
<td>18 (15.4)</td>
<td>1.35 (0.79-2.31)</td>
<td>1.45 (0.83-2.54)</td>
<td>1.54 (0.87-2.71)</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>610 (65.9)</td>
<td>83 (70.9)</td>
<td>1.27 (0.83-1.93)</td>
<td>1.25 (0.81-1.93)</td>
<td>1.33 (0.86-2.07)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td>225 (24.3)</td>
<td>24 (20.5)</td>
<td>0.80 (0.50-1.29)</td>
<td>0.85 (0.52-1.37)</td>
<td>0.87 (0.54-1.43)</td>
</tr>
</tbody>
</table>
### Associations between Discoid Lupus and SLE criteria/ESRD (SLE patients with DLE vs. those without DLE)

<table>
<thead>
<tr>
<th>SLE Manifestation</th>
<th>Adjusted OR (95% CI)</th>
</tr>
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<tr>
<td>Anti-Smith</td>
<td>2.41 (1.58-3.69)*</td>
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</tr>
<tr>
<td>Proteinuria</td>
<td>0.77 (0.47-1.27)</td>
</tr>
<tr>
<td>Casts</td>
<td>0.57 (0.27-1.20)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.24 (0.50-3.05)</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>1.33 (0.86-2.07)</td>
</tr>
</tbody>
</table>

† No 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
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

<table>
<thead>
<tr>
<th>N=892</th>
<th>Alive</th>
<th>Deceased</th>
<th>p=0.86</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DLE</td>
<td>710 (90%)</td>
<td>79 (10%)</td>
<td></td>
</tr>
<tr>
<td>DLE</td>
<td>94 (91.3)</td>
<td>9 (8.7%)</td>
<td></td>
</tr>
</tbody>
</table>

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