Lupus Skin Teleconference

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Overview

- Epidemiology
- Clinical classification
- Diagnosis, Causes
- Development of a disease severity measure (CLASI)
- Systematic epidemiologic, translational, and clinical studies
- Approaches to therapy
Incidence of Cutaneous LE

- 156 patients with newly diagnosed CLE (100 females and 56 males)
- Incidence: 4.3 (95% CI 3.62-4.98) per 100,000
- Prevalence: 73.24 (95% CI, 58.29-88.19) per 100,000
- 19% progression to SLE
- Incidence of cutaneous lupus about as frequent as SLE

*Durosaro et al, Arch Dermatol 145:249, 2009*
Challenges of Current ACR Classification
Criteria for SLE: Issues of case definition of
Cutaneous LE vs SLE

- Butterfly rash
- Discoid lupus
- Photosensitivity: Definition unclear
  - Better to have specific terminology for types of skin lesions induced
- Oral ulcers: Overlap with Discoid LE
ACR Dermatologic Criteria for SLE

• Many dermatologic criteria
  - Can meet SLE criteria with only dermatologic criteria or with no significant systemic disease *(Parodi and Rebora, Dermatol 194:217, 1997)*

QoL (Skindex): Cutaneous Lupus vs Other Diseases

QoL in Skin lupus

- Cutaneous lupus has a large impact on emotional quality of life
- Impact on emotional function is worse than hypertension, recent heart attack, or type II diabetes
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Cutaneous LE

- **LE-specific**
  - Skin biopsy shows LE-specific histology
  - Diagnosis of LE can be confirmed regardless of if ACR criteria for SLE are present

- **LE-nonspecific**
  - Not histopathologically distinct for LE and/or may be seen as a feature of another disease process
LE-nonspecific Skin Lesions

- Chronic Cutaneous LE
  - DLE: localized, generalized, hypertrophic
  - Lupus panniculitis
  - Tumid LE
- Subacute Cutaneous LE
- Acute cutaneous LE
DLE
Skin Disease in Lupus Erythematosus

- Inflammatory skin disease found in up to 70% of patients with SLE (Patel and Werth, Derm Clin 19:583, 2000)
LE-nonspecific Skin Lesions

- Usually in the active phase of the disease
- Those with LE-nonspecific lesions had increased disease activity when compared to those with only LE-specific lesions and to those with both kinds of lesions (Aecevic et al, Lupus 10:364, 2002).
Prognostic Significance of Cutaneous LE

Skin Disease only

- Generalized DLE
  - Localized DLE
  - Hypertrophic LE
  - LE Panniculitis
  - Tumid LE

SCLE

Systemic Disease

- Acute cutaneous LE
- LE-nonspecific skin disease
Overview

- Epidemiology
- Clinical classification
- **Diagnosis and Causes**
- Development of an disease severity measure (CLASI)
- Systematic epidemiologic, translational, and clinical studies
- Approaches to therapy
Diagnosis of Cutaneous Lupus

- Clinical findings
- Skin pathology: biopsy
- Occasionally look for antibodies in skin
- Specific lupus antibodies: may or not be present
  - Anti-nuclear antibody
  - Anti-SSA, SSB
  - Anti-dsDNA
  - Anti-histone
Diagnosis of Cutaneous Lupus

- Some people that have lupus antibody but don’t have lupus: not a specific test
- If suspect systemic lupus, will check for involvement of other organs
  - Urinalysis
  - Kidney function
  - Blood counts (anemia, low WBC, low platelets)
- Many with skin lupus don’t have systemic disease, but should be checked periodically
Diagnosis of Cutaneous Lupus

- If skin flaring, may be good time to have other blood tests checked
- Should touch base with your doctor with flares
Drug-induced Cutaneous LE

Thiazide diuretics
Calcium channel blockers
Antifungals
  Terbinafine (Lamisil), griseofulvin
Beta blockers
  oxyprenolol
NSAIDS: Piroxicam, naproxen
Antihistamines: Cinnarizine
Chemotherapy: Taxotere, Paclitaxel

ACE inhibitors
  Cilazapril, captopril
GI Acid inhibitors
  Ranitidine, omeprazole
TNF-α inhibit. biologics
  Etanercept, infliximab
Platelet inhibitor: Ticlopidine
Miscellaneous:
  Interferon α&β, statins, procainamide, phenytoin, oxyprenolol, d-penicillamine, fertilizer/pesticides
Causes

- Genetics
  - Complement deficiency
  - HLA types
  - Other genetic risks related to inflammatory pathways

- Smoking

- Ultraviolet light
Smoking and Refractory Cutaneous LE

n=114
P=0.006

Insights into Disease Classification

• Dissecting differences between types of cutaneous LE (and between patients) will likely be increasingly important in learning more about causes of cutaneous lupus
Overview

- Clinical
- Pathophysiology
- Development of a disease severity measure (CLASI)
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**Cutaneous LE Disease Area and Severity Index (CLASI)**

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion.

### Extent

<table>
<thead>
<tr>
<th>Anatomical Location</th>
<th>Activity</th>
<th>Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Ear</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Nose (incl. malar area)</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Rest of the face</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>V-area neck (frontal)</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Post Neck &amp;/or shoulders</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Chest</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Back, buttocks</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Arms</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Hands</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Legs</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
<tr>
<td>Feet</td>
<td>0-absent</td>
<td>0-absent, 0-dyspigmentation</td>
</tr>
</tbody>
</table>

### Mucous membrane

- Mucous membrane lesions (examine if patient confirms involvement)
  - 0-absent
  - 1-leision or ulceration

### Dyspigmentation

- Report duration of dyspigmentation after active lesions have resolved (record by patient — box appropriate box)
  - 0-absent, 0-dyspigmentation
  - 1-scaling
  - 2—severely atrophic scaling or panniculitis

- Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)
  - Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

### Alopecia

- Recent hair loss (within the last 30 days / as reported by patient)
  - 1-Yes
  - 0-No

- Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the hair lobes. A quadrant is considered affected if there is a lesion within the quadrant.

- Alopecia (clinically not obviously scarred)
  - 0-absent
  - 1-diffuse, non-inflamatory
  - 2-focal or patchy in one quadrant;
  - 3-focal or patchy in more than one quadrant

- Scarring of the scalp (judged clinically)
  - 0-absent
  - 1-one quadrant
  - 2-two quadrants
  - 3-three quadrants
  - 4-six quadrants
  - 5-affects the whole skull

### Total Activity Score

(For the activity score please add up the scores of the left side i.e. for erythema, scale/hyper trophy, mucous membrane involvement and alopecia)

### Total Damage Score

(For the damage score please add up the scores of the right side, i.e. for dyspigmentation, scarring/atrophy/panniculitis and scarring of the scalp)
Disease severity measure (CLASI)

- Many validation studies over past 6 years to make sure it measures reliably and responds to change with treatment
- Can study effects of new medications on skin
Overview

- Epidemiology
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Correlation of Disease Severity (CLASI) with Quality of Life (Skindex)

Klein et al., J Am Acad Dermatol 2011;64:849-58
QoL in Photosensitivity

Foering et al, JAAD, in press
Incidence of Refractory Disease

Moghadam-Kia and Werth, Arch Derm 145:255, 2009
Subsets of CLE with Refractory Disease

Moghadam-Kia and Werth, Arch Derm, 145:255, 2009
Conclusions

- Patients with generalized DLE are more refractory to current therapies than those with localized DLE or SCLE
- Smokers more refractory to all treatments
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Treatment of DLE, SCLE, Tumid LE, LE, Panniculitis

- Heat avoidance
- Drug Avoidance
- Sunscreens
  - UVB #30 or greater
  - Mexoryl
  - Helioplex
  - Physical Blockers (Titanium, Zn Oxide)
Treatment of Cutaneous LE

- Topical Steroids
- Topical nonsteroidal T cell inhibitors
  (Heffernan M et al, Arch Dermatol 141:1170, 2005)
  - Tacrolimus (Protopic)
  - Pimecrolimus (Elidel)
- Intraleisional Steroids
Treatment of Cutaneous LE

- Check 25-hydroxy Vitamin D level

Evidence for Systemic Therapy in CLE

- Frequently low Vitamin D in CLE
- OR 3.47 for Vitamin D deficiency
- Disease activity improved in treatment group (p=0.003)

Cutillas-Marco E et al, Lupus 23:615, 2014
Antimalarials

- Hydroxychloroquine <6.5 mg/kg/day
- Chloroquine <3.5 mg/kg/day
- Quinacrine 100 mg/day

- Hydroxychloroquine for 6-8 weeks
- If no better, add quinacrine 100 mg/day for 6-8 weeks
- Switch from Hydroxychloroquine to Chloroquine if still not improved
Antimalarials

- 10% had very low blood HCQ, considered noncompliant
- Combination antimalarials (HCQ or Chloroquine, + Quinacrine) work frequently when HCQ alone doesn’t work (Chang A et al, Arch Dermatol 147:1261, 2011)
Antimalarials in Cutaneous LE

Chang et al, JID Arch Dermatol, in press.
Other Therapies for Cutaneous LE

- Dapsone
- Retinoids
- Thalidomide
- Methotrexate, CellCept, Azathioprine
- Corticosteroids
Mycophenolate Mofetil Trial

Mycophenolate Mofetil Trial

Fig 3. Course of Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients with subacute cutaneous lupus erythematosus treated with mycophenolate sodium. tx, treatment.

Thalidomide in CLE

- 60 patients, ≥18 years old, Barcelona, Spain
- Effectiveness up to 80-90%
- Improvement starts in 2 weeks, with full effects in 4-8 weeks
- Highest response in SCLE and DLE (>90%), lowest in lupus profundus (50%)
- No difference in response in localized vs generalized DLE

*Cortes-Hernandez J, Br J Dermatol 2012;166(3):616-23*
Thalidomide in CLE

• High rate of relapse (70%), especially in DLE in 4-8 months after stopping treatment
  – SCLE relapse rate 24%
  – DLE relapse rate 84%
• Respond to retreatment
• 16% require maintenance
• Side effects: drowsiness, paresthesia (18%), reversible amenorrhea, stroke, teratogenicity

Cortes-Hernadez J, Br J Dermatol 2012;166:616-23
Thalidomide Analogues

- Up to 50,000 times more active than thalidomide
- Potentially less neurotoxicity
- Have complex mechanisms of action that need to be evaluated in context of clinical trials for specific subsets of diseases
CLASI activity change over time

Time (weeks) Braunstein and Werth, Arch Derm 66:571, 2012
CLASI lupus activity change over time

15 patients
86% with CR

Biological Modifiers in Photosensitive LE: Potential Targets

• Anti-Cytokines (Anti-IFNα, −IFNγ)

• T cell directed therapy (Anti-CTLA4, anti-CD4)

• B cell directed therapy (Anti-CD20, Rituxamab; Anti-Blys/April)

• Chemokine antagonists

• Anti-adhesion molecules
Other New Treatments


• Individual reports or case series: Rituximab (bullous LE), alitretinoin, polypodium leucotomias

• Sirukumab (anti-IL-6): negative result (*Szepietowski JC, Arthritis Rheumatism* 65:2661, 2013)
Rituximab

- 82 SLE patients received rituximab
  - 32 with significant skin disease before or after treatment
- 10/29 (39%) with baseline skin disease had beneficial skin response at 6 months
  - 6/14 (43%) with good response in ACLE
  - 0/8 (0%) with CCLE

Vital EM et al, Arthr Rheumotol, in press
Rituximab

- Flares of SCLE and CCLE occurred in 12 patients who had no skin disease orACLE at baseline

Vital EM et al, Arthr Rheumatol, in press.
Other new treatments

- Anti-IFNα monoclonal antibody (Sifalimumab)
- Anti-IFN receptor monoclonal antibody
- Apremilast (PDE4 inhibitor)-study completed
- Many more approaches in the pipeline
Skin Response with Sifalimumab Treatment: mITT Population

Secondary endpoint:
CLASI response in patients with moderate-to-severe skin involvement

% with a CLASI ≥10 at baseline achieving a ≥4 point reduction

Study week

CLASI responders (%)

Placebo (N=35)
Sifalimumab 200 mg q4w (N=33)
Sifalimumab 600 mg q4w (N=33)
Sifalimumab 1200 mg q4w (N=26)

Baseline

Week 24
(Sifalimumab 600 mg)

Baseline

Week 40
(Sifalimumab 1200 mg)

Khamashta, M et al, ACR, 2014
Other new treatments

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Biological Modifiers in Photosensitive LE: Potential Targets

• Increasing interest in looking at skin as outcome in studies

• If have refractory disease, important to participate in studies to determine potential new treatments
Summary

• Better understanding about epidemiology and clinical subsets of cutaneous lupus
• Outcome measure (CLASI)
• More options for therapeutically resistant patients
• Potential new therapies in the pipeline