Cutaneous Manifestations of Systemic Diseases

By: Dr. Mona Halawani
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Lupus Erythematosus
Classification – Le Spectrum

Chronic:

1. **DLE**
   - Isolated
   - Part of SLE -25%

- 5% of CUT. DLE ➔ SLE
- Koebnerize
- Rare Complic. ➔ S.C.C
- Localized Or Generalized
Variants Of DLE: - Hypertrophic Le

- Acral Le
- Tumid: - On face, trunk : Intdurated, Erythematous Odematous plaques without the overlying characteristic epidermal changes of DLE.

2) Lupus Panniculitis:

- Occur either with SLE or independently
- Tender nodules atrophy, Ulc.
Acute Cutaneous Le (SLE)

Specific:

1. Malar Rash
   - 1/3 – 2/3 of SLE
   - Macular Erythema
   - Raised indurated confluent plaques of Erythema with distinct borders.
   - Papular
   - Vesicular
   - Discord Lesions in Malar distribution
   - Spare Nasolabial folds
2. Photosensitivity in 50% of SLE

3. Oral Lesions 20 – 25% of SLE
   - Petechia
   - Gingivitis
   - Cheilitis
   - Ulcers (on hard palate), Buccal Mucosa, lips, nasal, Conjunctival, Vaginal & Perianal Mucosa.

4. Discord Lesions
Non-specific Lesions

1. Scarring Alop.
   - 30% of SLE: Reversible Gen. Alop.
   - Lupus hairs

2. Vascular

A) Vasculopathy:
   - Raynaud’s Phenomenon
   - Preiungnal Erythema, Palmar Erythema, Nail Fold Capillary Changes.
   - Livedo Reticularis – Evaluate for underlying Antiphospholipid Synd.
   - Chilblain or Perniosis
B) **Vasculitis:**

- Palpable Purpura, Necrosis, Ulceration
- Urticarial Vasculitis

3) Angioedema

4) Rheumatoid Nodule

5) Calcinosis Cutis

- Bullons SLE < 2% in SLE
Lupus Subsets

- Sub Acute Cutaneous Lupus Erythematosus (SCLE), 10% of Lupus cases.
  - More persistent than ACLE, weeks to months
  - Photodistributed
  - Annular
  - Papulosquamous, Non-scarring
  - Triggered or worsened by Thiazide
  - Good prognosis
  - Minimal Kidney or Cns involv., Mild Systemic lesions
  - Anti Ro Abs: 70%, Anti La: 25%
**Neonatal LE (NLE)**

- Occurs in neonates of mothers who have or will develop Ct. Dis.
- SCLE – Like Lesions – Improves in 4-6 M- 40%
- **50%**: Congenital heart block
- **10%**: Both Cardiac & Cutaneous
- **Minority**: Hepatic, Hematologic, Neurologic
- Anti Ro Abs: In Infants & Mothers, Antila, Anti U1 Rnp, Anti Cardiolipin.
### The 1982 Revised Criteria for Classification of Systemic Lupus Erythemaosus

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>1. Malar rash</strong></td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
</tr>
<tr>
<td><strong>2. Discord rash</strong></td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.</td>
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<tr>
<td><strong>3. Photosensitivity</strong></td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation.</td>
</tr>
<tr>
<td><strong>4. Oral ulcers</strong></td>
<td>Oral or nasopharyngeal ulceration, usually painless observed by a physician.</td>
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<tr>
<td><strong>5. Arthritis</strong></td>
<td>Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion.</td>
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</tbody>
</table>
| **6. Serositis** | Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion  
  Or  
Percarditis: documented by ECG or rub or evidence of pericardial effusion. |
| **7. Renal disorder** | Persistent proteinuria greater than 0.5 gm per day or greater than 3 + if quantification not performed.  
  Or  
Cellular cases: may be red cell, hemoglobin, granular, tubular, or mixed. |
### The 1982 Revised Criteria for Classification of Systemic Lupus Erythematosus (Continued)

| 8. Neurological disorder | Seizures: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance)  
Or  
Psychosis: in the absence of offending drugs or known metabolic derangements (e.g., uremia, ketoacidosis, or electrolyte imbalance) |
|--------------------------|---------------------------------------------------------------------------------------------------------------|
| 9. Hematologic disorder  | Hemolytic anemia: with reticulocytosis  
Or  
Leukopenia: less than 4000/mm³ total on two or more occasions  
Or  
Lymphopenia: less than 1500/mm³ on two or more occasions  
Or  
Thrombocytopenia: less than 100,000/mm³ in the absence of offending drugs |
| 10. Immunologic disorder | Positive LE cell preparation  
Or  
Anti-DNA: antibody to native DNA in abnormal titer  
Or  
Anti-Sm: presence of antibody to Sm nuclear antigen  
Or  
False-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test |
| 11. Antinuclear antibody | An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome. |
# Autoantibodies in SLE and LE Subnets

<table>
<thead>
<tr>
<th>Serology</th>
<th>SLE(^{146})</th>
<th>DIL(^{145})</th>
<th>SCLE(^{64})</th>
<th>DLE(^{144})</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>99%</td>
<td>&gt;99%</td>
<td>80%</td>
<td>35%</td>
</tr>
<tr>
<td>Histone</td>
<td>70%</td>
<td>&gt;95%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>dsDNA</td>
<td>50%</td>
<td>0</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>RNP</td>
<td>35%</td>
<td>0</td>
<td>5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Sm</td>
<td>30%</td>
<td>0</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>SSA/Ro</td>
<td>30%</td>
<td>0</td>
<td>70%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>SSB/La</td>
<td>15%</td>
<td>0</td>
<td>25%</td>
<td>NR</td>
</tr>
</tbody>
</table>
Workup For Suspected Cutaneous LE (DLE, SCLE, SLE)

- Biopsy for histology: lesion
- Biopsy for immunofluorescence: old lesion

If either is consistent with LE:

- System review
- ANA
- nDNA
- Antibodies-SSA (Ro), SSB (La), Sm, nRNP
- Urinalysis
- ESR, CBC
- C3 C4 CH₅₀
# Treatment of DLE and SCLE

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sun avoidance</td>
<td>a. Antimalarials:</td>
</tr>
<tr>
<td>2. Sun blocks</td>
<td>1) Hydroxychloroquine (Plaquenil)</td>
</tr>
<tr>
<td>3. Protective clothing</td>
<td>2) Chloroquine (Aralen)</td>
</tr>
<tr>
<td>a.</td>
<td>3) Quinacrine (Atabrine)</td>
</tr>
<tr>
<td>b.</td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td></td>
</tr>
<tr>
<td>Local therapy</td>
<td>a. Corticosteroids, topical</td>
</tr>
<tr>
<td>2.</td>
<td>b. Corticosteroids, injectable</td>
</tr>
<tr>
<td>a.</td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of SLE

Mild Disease

- Education (for all patients)
- Rest (for fatigue and malaise)
- Sun avoidance/protection (for photosensitivity, DLE)
- Physical therapy (for range of motion and strength)
- NSAIDs (for joint/body pain)
- Antimalarials (for skin involvement, joint pain, malaise, fatigue and fever)
- Prednisone (low-doses: 2.5 - 10 mg per day for joint pain)
Severe disease with End-Organ Damage

- Prednisone (high-dose: 60 mg per day)
- Addition of steroid-sparing agent
  - Azathioprine, cyclophosphamide
    (methotrexate, chlorambucil, cyclosporine)
Scleroderma

- Chronic Dis. That involves the Microvasculature and connective tissue and results in fibrosis. It may be localized as in morphea or more generalized and involving visceral organs as in progressive systems sclerosis.
Systemic Scleroderma

Clinical Manif:

I- Cutan. Manif

1. Sclerosis of the skin
2. Raynaud’s phenomenon. 98% of SS, IST symptom in 70% of SS.
3. Telangiectasias on face and hands.
4. Calsinosis on palmar aspects of terminal phalanges.
5. ABN. Nail fold capillary pattern.
6. ULC. Over tips of fingers.
7. Hyper and hypopigmentation.
II – Systemic Manif:

1. GIT-most common, Esophageal Dysmotility, Dysmotility in small bowel and colon, regurgitation, malabs and peptic esophagitis.

2. Plum. Dis.: Pulm fibrosis or pulm hypertension with right side H.F.

3. Renal Dis.: renal Dis. And hypertension are major causes of death in SS.

4. Musculoskeletal: Arthralgia or Arthritis, Myositis.

5. Cardiac. Dis.:
   - 35% of SS: Pericardial effusion
   - 30% - 50%: Myocardial fibrosis
II- Systemic Manif: Contu

6. CNS: Uncommon

7. Hematologic ABN.: Common

- Renal Disease
- 27%: - Anemia
- Bleeding GIT Telangiactases

Localized Scleroderma

- Localized Sclerosis of skin, subcutaneous tissue and occasionally underlying muscles.

Clinical Features:
- Plaque lesions
- Guttate
- Linear
- Subcutaneous (Morphea Profunda)
- Fronto parietal lesions (EN COUP DE SABRE)
Dermatomyositis

- Polymyositis: is a similar Dis. Without skin lesions.

**Classification:**

1. Polymyositis
2. Dermatomyositis
3. PM or DM associated with malignancy
4. Childhood DM
5. Overlap syndromes (with other CT.Dis).
6. Amyopathic DM.(DM sine Myositis)
Clinical Features:

1. Cutaneous Manifestations
   
   A) Pathognomonic signs
   
   1) Gottron’s Papules
   
   2) Gottron’s sign
   
   3) Heliotrope (Violaceous) Erythema

   B) Other signs:
   
   1) Periungual Telangiectasia with ragged cuticle
   
   2) Poikiloderma
   
   3) Calcinosis, common in children
   
   4) Photosensitivity
II – Skeletal Muscle Affection

III – Systemic Manif. rare in contrast to SLE & SS

**Associations:**

- DM ASS. With malig. In adult patients
- Increase incidence of ovarian tumors.

**Diagnosis:**

- History, Physical Exam.
- CBC, ESR, increase creatine kinase
- EMG
- ANA, ANTI Jo-1-Pulm. Fibrosis
- Anti M1-2-D.M. (20%)
- Biopsy
Diagnostic Criteria for PM/DM:

1. Proximal symmetric progressive muscle weakness
2. Increase skeletal muscle enzyme, CPK, Aldolase, S.Got, SGPT, LDH.
3. Abnormal muscle biopsy
4. Abnormal EMG
5. Typical Cutaneous lesions (for DM) (3-4 OUT OF 5)
Treatment:

- Bed rest.
- Physical Therapy.
- Skin disease: Topical steroid, Hydroxy chloroquine, systemic steroid.
- Muscle disease: Systemic steroid, Methotrexate, Azathioprine, I.V. Gamma-Globulin.
- Cyclophosphamide, Chlorambucil, CSA.
Cutaneous Manifestations of Diabetus Mellitus:

I- Skin diseases with strong associations others with less distinct associations.

II- Cutaneous infections

III- Cutaneous manifestations of diabetic complications.

IV Skin reactions to diabetic treatment.
I – Cutaneous Disease Association with DM.

- **Necrobiosis Lipoidica Diabeticorum (NLD)**
  - Cut marker of DM.
  - 0.3% of DM.
  - 60% of NLD have DM, 20% glucose intolerance.
  - Site.
  - Persistence independent of glycemic control.
  - Complications:- Ulc.
  - Pathogenesis.
  - Rx
Grannloma Annulare.

DM is found more frequently in adult onset GA, generalized or perforating GA.

Diabetic Dermopathy (Shin spots)

Site
30 – 60% of DM.
20% - non diabetic
Pathogenesis

Diabetic Thick Skin.
Scleredema Diabeticorum
- long standing DM, obesity.
Acanthosis nigricans:
- Site
- Most cases associate with insulin resistance.
- Other causes of AN.

Perforating disorders.
- Site
- In renal failure, IDDM, NIDDM.

Eruptive xanthomas:
- Site
- Untreated DM, severe hypertriglyceridemia.

Diabetic bullae:
- Site: lower extremities
  - Painless, non pruritic, tense, falccid
  - No immunopathologic features
  - Dx by exclusion
II – Cut. Infections ass. with DM:

- Predisposing factors for infections
- Fungal and yeast infections

- Candida infections
  Early indicators of undiagnosed DM intertrigo, Vulvovaginitis, Paronychia, Onychomycosis, angular cheilitis.

- Anogenital itching

- Generalized itching is not a feature of DM

- Mucormycosis
  Diabetic KIA is a risk factor.
Bacteria Infections

- Erythrasma, caused by Corynebacterium minutissimum.
- Group B Streptococcal infections skin, soft tissue, bone.
- Group A Streptococcal infections.
  - 3.7 fold greater in DM
  - Soft tissue infections.
- Staphyloccocal infections
- Malignant external otitis.
  - Caused by Pseudomonas
  - Fatal outcome
- Necrotizing fasciitis
III – Cutaneous Compl. Ass. with DM:

- Macroangiopathy
- Microangiopathy
- Neuropathy
IV – Cutaneous Reactions to Diabetic Treatment

- Allergic reactions 1-5% of patients taking sulfonylureas
  - Maculopapular
  - Photoallergic
  - Lichenoid
  - Rosacea like

- Glucagonoma syndrome.
  - Rare, paraneoplastic synd.
  - DM, erosive rash (necrolytic migratory erythema), glossitis, wt. loss, diarrhea, anemia, hypoalbuminemia

- **Cause:** glucagon-secreting pancreatic tumor, alpha islet cells.
Cutaneous Manifestations of Thyroid Disease

Cut manif. Of hypothyroidism.

- Skin:- cold, dry, pale, xerosis, pruritus, eczema craquele acquired Keratoderma. Carotenemia, diffuse alopecia, loss of hair on lat. Eyebrows, nails changes. The most charac.sign- generalized myxedema.
- Cutaneous manif. of hyperthyroidism.
  - opposite of hypo.
  - onycholysis
  - Pruritus
  - Pretibial myxedema.
- In 0.4 – 4% of patients with graves disease.
Pruritus

- Def
- What is the classic mediator of Itch?
- What others Itch – producing mediators in skin?
  - Serotonin
  - Endopeptidases
  - Neuropeptides
  - Eicosanoids
- How would you approach the patient with Pruritus?
  - Detail history
  - Ass. Skin lesions
  - Exam lesion
  - Secondary skin lesion (excoriations, lichenifications)
What are the questions to ask of a Pruritic patient with no primary skin lesion?

- Is the Itch loc. Or Gen?
- When is the Pruritus more severe?
- How long does it last?
- Relationship to activities (e.g. bathing)
- Does he scrub excessively?
- Occupational exposure.
- Drug history
- General health
- Foreign travel
- Does the patient have any pets?

Which skin disease with primary skin lesions are characterized by marked Pruritus?

- Arthropod reactions, LP, BP, DH, CD, drug eruptions, urtic.
What is important on the Physical exam in a patient with pruritus but no Primary or only secondary skin lesions?
- Exclude xerosis
- Lymphadenopathy, hepatosplenomegaly (Lymphoma)
- Rectal, pelvic exam.

Investigation of Pruritus with no rash:
- CBC, diff for eosinophilia
- LFT, AP, HCV-AB, Hep.B –S- AG.
- Renal profile
- Urine analysis
- FBS
- Protein electrophoresis
- Immuno electrophoresis
- Stool for O & P, occult blood
- Thyroid function
- PAP smear
- CXR
- CT scan of Abd.- R/o Lymphoma.
What is Uremic Pruritus?
- Itch of chronic not acute renal failure.
- Affects 20-50% of patients especially those on dialysis
- Pathophysiology: multifactorial

Rx:
- Emollient
- UVB phototherapy
- Erythropoietin
- Antihistamines
- Topical capsaicin
- Activated charcoal
- Cholestyramine
- Naltrexone
- Parathyroidectomy
- Ondansetron
Pruritus of cholestasis.
  - highly distressing and persistent
Rx:-
  - Cholestyramine
  - Rifampicin
  - Antihistamine
  - Naltrexone, Nalmefene, Naloxone

Which hematologic malignancy is well known to present with pruritus?
  - Hodgkins disease
  - Pruritus may precedes the diagnosis by as many as 5 years.
What other hematologic diseases present with Pruritus?

- Sezary syndrome (T-cell leukemia)
- Polycythemia vera, 50% of patients, exacerbated by contact with water
- Mastocytosis
- Myeloid and Lymphatic leukemia.

Which endocrine disorders present with itching?

Which endocrine disorder is commonly associated with anogenital Pruritus?
Erythema nodosum

- Def
- Epidemiology
  - The most common type of Panniculitis
  - Peak age 20 -30 years
  - ♂ > ♀

- Etiology
  - EN is a reactive hypersensitivity reaction that may occur in response to a number of antigenic stimuli.
# Causes of Erythema Nodsum

<table>
<thead>
<tr>
<th>Infections</th>
<th>Others</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
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<tr>
<td>St. coc</td>
<td></td>
<td>Sulfonamides OCP</td>
</tr>
<tr>
<td>T.B.</td>
<td></td>
<td>Others: Minocin, Gold, penicillin</td>
</tr>
<tr>
<td>Yersinia</td>
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</tr>
<tr>
<td><strong>Fungal</strong></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Coccidioidomycosis, blastomycosis, sporotrichosis, histoplasmosis, dermatophytosis.</td>
<td></td>
<td>Sarc.</td>
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<tr>
<td><strong>Viral</strong></td>
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<tr>
<td><strong>Others</strong></td>
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<tr>
<td>Amebiasis, giardiasis, ascariasis</td>
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</table>
Clinical Manifestations

Invest:-

- Careful history
- CBC, ESR
- Throat swab
- ASO
- Tuberculin test
- CXR
- Viral titres
Rx:-

- Bed rest
- NSAID
- Potassium iodide
- Colchicine
- Hydroxychloroquine
- Prednisolone
- Dapsone