CUTANEOUS MARKERS OF SELECTED IMPORTANT CONNECTIVE TISSUE DISEASES

Dr. Sami N. Alsuwaidan

President, Saudi Society of Dermatology & Dermatologic Surgery

Consultant in Dermatology & Cutaneous Laser Surgery

College of Medicine, King Saud University

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

TYPES OF CUTANEOUS LUPUS

There are several variants of cutaneous lupus, defined in part by the location and depth of the inflammatory infiltrate

Acute cutaneous lupus

involves primarily the epidermis and upper dermis and is usually associated with systemic disease

Subacute cutaneous lupus

involves primarily the epidermis and upper dermis and is associated with anti-Ro/SSA autoantibodies and photosensitivity; the majority of patients do not have significant systemic disease

Discoid lesions of lupus

involve the epidermis, upper and lower dermis, and adnexal structures, and they can scar; the majority of patients do not have significant systemic disease

TYPES OF CUTANEOUS LUPUS

Lupus erythematosus tumidus

Involves the dermis but there is no prominent epidermal or adnexal involvement

Lupus panniculitis

Involves the subcutaneous tissue and may result in disfiguring depressed scars

CUTANEOUS FINDINGS (NON-SPECIFIC) OF SYSTEMIC LUPUS ERYTHEMATOSUS

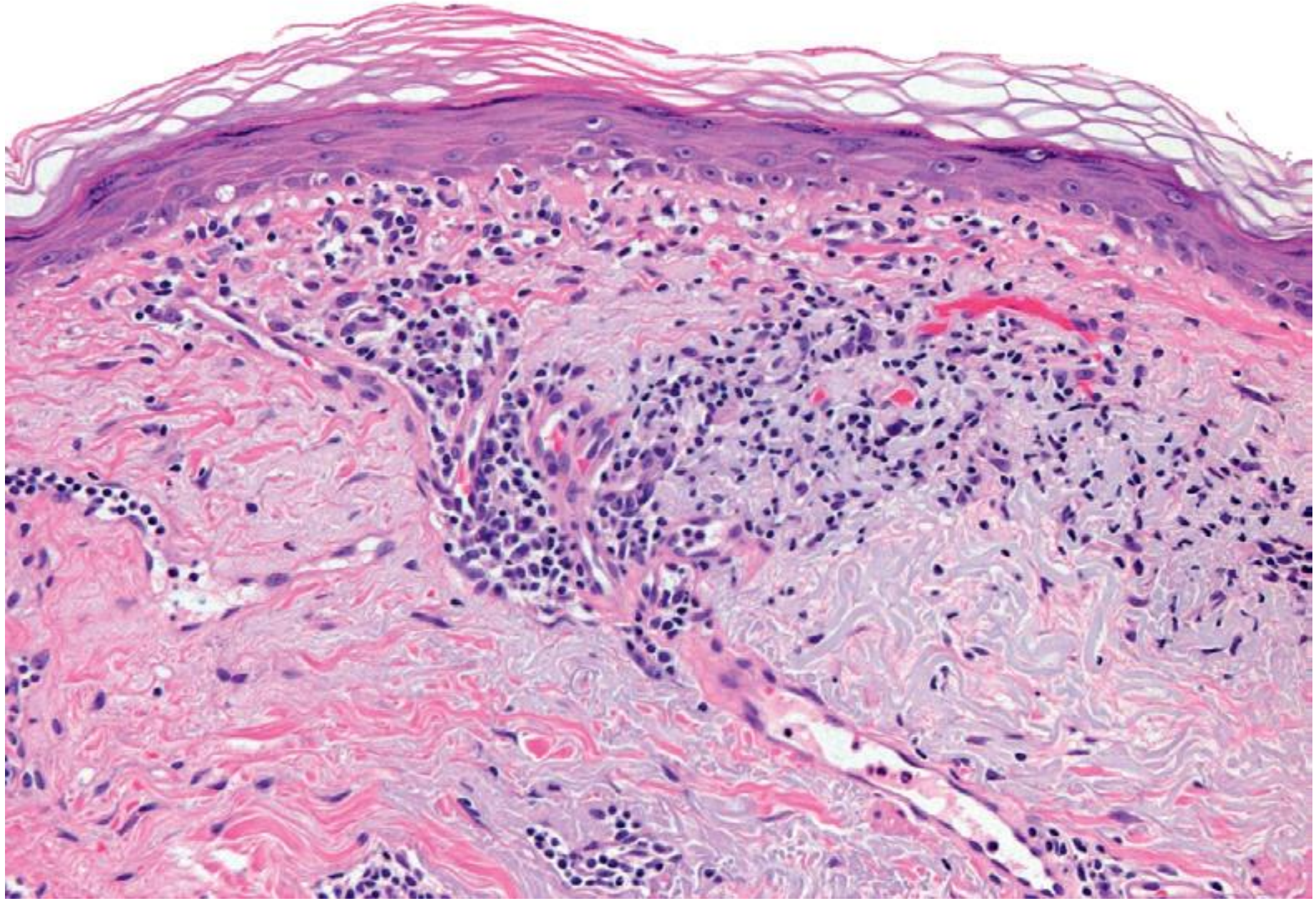
- Diffuse non-scarring alopecia
- Raynaud's phenomenon
- Nailfold telangiectasias and erythema
- Vasculitis:
    - Urticarial vasculitis
    - Small vessel vasculitis (e.g. palpable purpura)
    - Polyarteritis nodosa-like lesions
    - Ulcerations
- Cutaneous signs of antiphospholipid syndrome:
    - Livedo reticularis
    - Ulcerations
    - Acrocyanosis
    - Atrophie blanche-like lesions
- Livedoid vasculopathy
- Palmar erythema
- Papular and nodular mucinosis

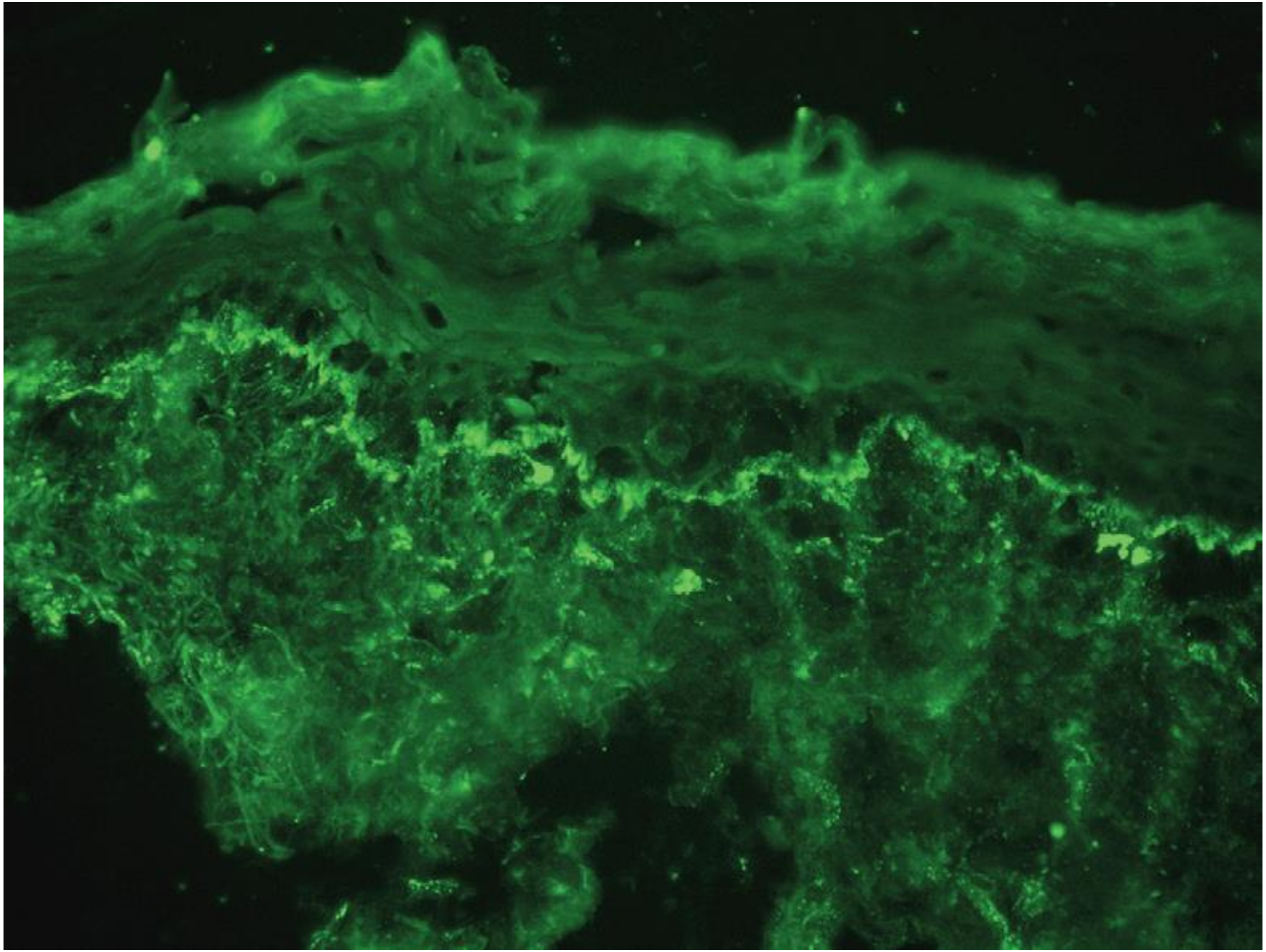
EVALUATION FOR SYSTEMIC LUPUS ERYTHEMATOSUS

- **HISTORY**
- **PHYSICAL EXAMINATION**
    - **Specific cutaneous lesions**
    - **Nonspecific cutaneous lesions**
    - **Lymphadenopathy, arthritis**
- **LABORATORY TESTS**
    - **ANA with profile (anti-dsDNA, -Sm)**
    - **Urinalysis**
    - **CBC with differential, platelet count**
    - **Chemistries (BUN, creatinine)**
    - **Erythrocyte sedimentation rate**
    - **Complement levels (C3, C4)**

PATHOGENESIS

The pathogenesis of cutaneous LE is complex, and it involves an interaction between genetic and environmental factors. The latter include ultraviolet radiation (UVR), medications, and possibly viruses. This interplay triggers a complex inflammatory cascade of cytokine, chemokine and inflammatory cell responses that include cells residing within as well as recruited to the skin. Overall, the lichenoid tissue reaction, defined as epidermal basal cell damage and a band-like lymphocytic infiltrate in the upper dermis, characterizes most subsets of cutaneous LE.





THE AMERICAN COLLEGE OF RHEUMATOLOGY 1982 REVISED CRITERIA FOR CLASSIFICATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

1. Malar rash

Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds

2. Discoid rash

Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions

3. Photosensitivity Skin rash

as a result of unusual reaction to sunlight, by patient history or physician observation

4. Oral ulcers

Oral or nasopharyngeal ulceration, usually painless, observed by physician

5. Arthritis

Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion

6. Serositis

a) Pleuritis – convincing history of pleuritic pain, rubbing heard by a physician, or evidence of pleural effusion *OR*

b) Pericarditis – documented by ECG, rub or evidence of pericardial effusion

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7. Renal disorder

a) Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantitation not performed *OR*

b) Cellular casts – may be red cell, hemoglobin, granular, tubular or mixed

8. Neurologic disorder

a) Seizures – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance

OR

b) Psychosis – in the absence of offending drugs or known metabolic derangements, e.g. uremia, ketoacidosis or electrolyte imbalance

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9. Hematologic disorder

a) Hemolytic anemia with reticulocytosis

OR

b) Leukopenia – less than 4000/mm3 total WBC on two or more occasions

OR

c) Lymphopenia – less than 1500/mm3 on two or more occasions

OR

d) Thrombocytopenia – less than 100 000/mm3 in the absence of offending drugs

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10. Immunologic disorder

- a) Anti-DNA antibody to native DNA in abnormal titer
- *OR*
- b) Anti-Sm: presence of antibody to Sm nuclear antigen
- *OR*
- c) Positive finding of antiphospholipid antibodies based on: (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies; (2) a positive test result for lupus anticoagulant using standard methods; or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescenttreponemal antibody absorption test (FTA-ABS)

11. Antinuclear antibody

An abnormal titer of antinuclear antibody by immunofluorescence (or an equivalent assay) at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome.

THERAPY OF CUTANEOUS LUPUS

LOCAL THERAPY

- Sun protection
- Topical and intralesional corticosteroids
- Topical calcineurin inhibitors
- Topical retinoids

THERAPY OF CUTANEOUS LUPUS

SYSTEMIC ANTIMALARIAL THERAPY

- Hydroxychloroquine (200 mg po qd–bid in adults; up to 6.5 mg/kg ideal body
- weight/day)
- Chloroquine (125–250 po qd in adults; up to 3.5–4 mg/kg ideal body weight/day)
- Quinacrine (100 mg po qd)
- Combination of hydroxychloroquine or chloroquine and quinacrine

THERAPY OF CUTANEOUS LUPUS

SYSTEMIC THERAPY FOR ANTIMALARIAL-RESISTANT CUTANEOUS DISEASE

- **Retinoids (e.g. acitretin, isotretinoin)**
- **Thalidomide (50–100 mg po qd for clearing and, if necessary, 25–50 mg po qd–twice weekly for maintenance)**
- **Dapsone (primarily for bullous eruption of SLE)**
- **Immunosuppressive agents (e.g. mycophenolate mofetil, azathioprine)**
- **Sulfasalazine**
- **Clofazimine**
- **Systemic corticosteroids**
- **Immune response modifiers (e.g., rituximab, abatacept,* belimumab, anti-IL-6 Ab,**
- **anti-IL-10 Ab)**

DERMATOMYOSITIS

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Dermatomyositis is classified as one of the idiopathic inflammatory myopathies.

Is a disease of presumed autoimmune pathogenesis that presents with a symmetric, proximal extensor inflammatory myopathy and a characteristic cutaneous eruption

CLASSIFICATION SYSTEM FORDERMATOMYOSITIS

Adult-onset

- **Classic DM**
- **Classic DM with malignancy**
- **Classic DM as part of an overlapping connective tissue disorder**
- **Clinically amyopathic DM***
- **Amyopathic DM**
- **Hypomyopathic DM**

Juvenile-onset

- **Classic DM**
- **Clinically amyopathic DM**
- **Amyopathic DM**
- **Hypomyopathic DM**

CUTANEOUS MANIFESTATIONS OF DERMATOMYOSITIS (common)

- Heliotrope sign
- Eyelid edema
- Gottron's papules
- Gottron's sign
- Photodistributed poikiloderma (includes facial erythema)
- Scalp poikiloderma
- Non-scarring alopecia
- Nail fold changes (includes ragged cuticles, nail fold telangiectasias)
- Calcinosis cutis (especially in juvenile dermatomyositis)

CUTANEOUS MANIFESTATIONS OF DERMATOMYOSITIS (uncommon)

- Cutaneous erosions or ulcerations
- Holster sign (poikiloderma of the lateral thighs)
- Flagellate erythema
- Vesicobullous lesions
- Exfoliative erythroderma
- Panniculitis
- Gingival telangiectasias
- Pustular eruption of the elbows and knees
- Lipoatrophy (especially in juvenile dermatomyositis)
- Small vessel vasculitis (especially in juvenile dermatomyositis)

EVALUATION OF THE PATIENT WITH DERMATOMYOSITIS

HISTORY

Including potential triggers and previous malignancies, and a review of systems

PHYSICAL EXAMINATION

Skin, muscle and complete general examination

- **(including, in adults, breast and pelvic [women], testicular and prostate [men],**
- **and rectal [both sexes]**

EVALUATION OF THE PATIENT WITH DERMATOMYOSITIS

Laboratory evaluation

- ***Cutaneous*** **– Skin biopsy**
- ***Muscle*** **–**
- **Serum creatine kinase, serum aldolase, occasionally urine creatine†**
- **Electromyography (EMG);**
- **Muscle biopsy;**
- **MRI or U/S (if EMG or muscle biopsy are negative)**
- **SEROLOGY (ANTIBODIES)?!**

EVALUATION OF THE PATIENT WITH DERMATOMYOSITIS

- ***Pulmonary –***
- **Pulmonary function tests (PFTs) with CO diffusion**
- **Chest X-ray and/or high-resolution chest CT**
- ***Cardiac –***
- **Electrocardiogram (EKG)**
- **If symptomatic, echocardiogram and/or Holter monitor**
- ***Esophageal –***
- **If symptoms, barium swallow**
- ***General –***

Complete blood count, comprehensive metabolic panel with fasting levels of glucose and lipids‡, autoantibody panel

EVALUATION OF THE PATIENT WITH DERMATOMYOSITIS

Malignancy screen (adults)

- **Urinalysis, stool occult blood testing**
- **Serum prostate-specific antigen (PSA) [men]**
- **Serum CA125 [women]**
- **Mammogram and transvaginal pelvic U/S [women]**
- **CT of chest, abdomen and pelvis**
- **Colonoscopy, if age-appropriate, iron deficiency anemia, occult blood in stool, or symptoms**
- **Upper endoscopy – if colonoscopy negative in the setting of iron deficiency anemia, occult blood in stool, or symptoms**
- **If planning chronic systemic Corticosteroids DEXA bone density scan**

TREATMENT (CUTANEOUS)

- Sunscreens (high sun protection factor including protection against UVA)
- Topical corticosteroids
- Topical tacrolimus
- Hydroxychloroquine (200 mg twice daily; increased frequency of drug eruptions in patients with dermatomyositis)
- Hydroxychloroquine (200 mg twice daily) plus quinacrine (100 mg/day)
- Low-dose weekly methotrexate (5–15 mg weekly)
- Mycophenolate mofetil
- High-dose IVIg (2 g/kg/month)
- Retinoids, Dapsone, Thalidomide
- Leflunomide
- Antiestrogens (e.g. tamoxifen, anastrazole)
- TNF-α inhibitors (e.g. infliximab, etanercept)
- Rituximab

SCLERODERMA

SCLERODERMA

- SCLERODERMA
- SYSTEMIC SCLEROSIS
- PROGRESSIVE SYSTEMIC SCLEROSIS
- ACROSCLEROSIS
- CREST SYNDROME
- LOCALIZED SCLERODERMA
- LINERAR MORPHEA
- MORPHEA

SYSTEMIC SCLEROSIS

- **Systemic sclerosis (SSc, scleroderma) is an autoimmune connective tissue disease of unknown etiology that affects the skin, blood vessels and internal organs. The name *systemic sclerosis* is meant to convey the systemic nature of the disease, which has two major clinical subtypes: *limited* and *diffuse*.**
- **Limited SSc is characterized by fibrotic skin changes that are limited to the fingers, hands and face and includes the CREST syndrome.**
- **In diffuse SSc, generalized fibrotic skin changes are seen and they usually start in the fingers and hands but spread to involve the forearms, arms, trunk, face and lower extremities.**

SCLERODERMA

- More common in females
- 30-50 years
- Not hereditary (but could be familial)
- Not invariably progressive and fatal!!

1. Fingers can become white due to the lack of blood flow

2. The fingers may turn blue as the blood vessels dilate to keep the blood in the tissues

3. Finally the fingers may turn red as the blood begins to return

WORK UP

- Skin biopsy (histopathology)
- Serology (auto antibodies)
  - n RNP
  - RNA polymerase T (Scl 70)
  - Centromeres
  - Polymerase I

TREATMENT

- RAYNAUD’S PHENOMENON
- CUTANEOUS ULCERS
- FIBROSIS
- MORPHEA
- OTHER SKIN ISSUES
- INTERNAL ORGANS