Dermatologic Signs in Rheumatology

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WHAT IS SKIN FAILURE?

Failure of any organ system occurs when its normal tasks and functions can no longer be performed.

The same goes for the integument, which is the largest organ of the body. The skin plays many important roles. It acts as a physical barrier against trauma and aids in the prevention of foreign materials, including bacteria, from entering the body. Conversely, this barrier also prevents loss of body fluids and essential nutrients, such as protein and iron. Normally functioning skin also serves in temperature regulation, detection of sensation, toxin excretion, and vitamin D synthesis and as an immune modulator. When this organ loses the ability to maintain temperature control; when it can no longer retain the balance of fluids, electrolytes, and nutrition; and/or when it fails as a mechanical barrier, skin failure has occurred.
Many systemic rheumatologic conditions present with skin findings

The skin is a highly visible organ that is frequently affected in rheumatic diseases, and the presence of skin lesions may be helpful diagnostically
caveats

1st caveat, a major pitfall for the nondermatologist in evaluating skin lesions is incomplete knowledge of the entities in the differential diagnosis.

2nd caveat for the nondermatologist concerns skin biopsy. Being able to determine when a skin biopsy is likely to be diagnostically useful in many cases requires a great deal of specialized knowledge, as does the interpretation of pathology reports.
The differential diagnosis for skin findings may require a skin biopsy for clinical-pathologic correlation. The most common skin manifestations are neither specific nor pathognomonic for a single rheumatic disease but are seen with some frequency throughout rheumatic diseases e.g. Raynaud’s, alopecia, oral ulcers, skin ulcers, hyperpigmentation, and subcutaneous nodules
Skin rashes, skin ulcers, and other skin manifestations occur frequently in rheumatic diseases. In a few cases skin involvements are nearly pathognomonic of the underlying rheumatic disease (e.g., digital pitting scars and thickened skin of the fingers in systemic sclerosis, Gottron’s nodules or sign in dermatomyositis; dilatation and dropout of the nail fold capillaries in systemic sclerosis/dermatomyositis, and the butterfly rash of lupus)
Skin manifestations often assist in making the diagnosis of a rheumatic disease by narrowing the number of the diseases in the differential e.g., erythema nodosum, palpable purpura in the vasculitides, Keratoderma blennorrhagicum, and circinate balanitis in the spondyloarthropathies.
Skin manifestations serve, along with other cutaneous/noncutaneous manifestations, by becoming part of diagnostic or classification criteria for one or more rheumatic diseases e.g., oral mucosal ulcers along with vulval ulcers in Behcet’s, digital necrosis in a male smoker or digital necrosis in the vasculitides, discoid lesions in lupus, and salmon-colored rash of Adult Still’s Disease
Presentation of Skin Manifestations

In Rheumatic Diseases

Purpura
Erythema Nodosum
Malar Erythema
Livedo Reticularis
Telangiectasias
Ulceration
Panniculitis
Puffy Fingers
Chilblain Lupus Erythematosus
Purpura

Purpura is visible hemorrhage in the skin or mucous membranes

A circumscribed deposit of blood greater than 0.5 cm in diameter

palpable purpuric lesions
Palpable purpura
Cellulitis with signs simulating purpura fulminans
(Purpuric lesions can have varying degrees of associated inflammation)
Purpura fulminans and DIC
Differential Diagnosis of Purpura

Three main pathogenic mechanisms of purpura:

1. simple hemorrhage
2. inflammatory hemorrhage
(i.e., inflammation directed at the blood vessels)
3. occlusive hemorrhage with minimal inflammation
The morphology of purpura
(can be used to help to determine the most likely mechanism)

There are six morphologic subsets of purpura:

1. Macular petechiae
   (≤4 mm in diameter, flat, noninflammatory, type of “simple hemorrhage”)

2. Intermediate macular purpura
   (5–9 mm in diameter, flat, noninflammatory, type of “simple hemorrhage”)

3. Macular ecchymoses
   (≥1 cm in diameter, flat, noninflammatory, type of “simple hemorrhage”)

4. Palpable purpura
   (inflammatory purpura with prominent early erythema; round, port-wine color; partially blanches with diascopy indicating the presence of both inflammation and hemorrhage)

5. Noninflammatory retiform purpura
   (minimal early erythema; some lesions are palpable; typically due to microvascular occlusion)

6. Inflammatory retiform purpura
   (early lesions have prominent erythema; some lesions are palpable)
Approach to the Diagnosis of Purpura

(A) First determine if the lesion is:

Purpura?

Primary purpura?

(B) Determine if the lesions are palpable (exclude major trauma-induced hemorrhagic contusions):

1. If none are palpable – represents “simple hemorrhage” – classify by size
   (macular petechiae, ≤4 mm; intermediate macular purpura, 5-9 mm; macular ecchymoses, ≥1 cm).
2. If some are palpable, classify as one of the following:
   (a) Early lesions are round, port-wine colored, and have prominent erythema
      (partially blanch with diascopy) – represents palpable purpura (often due to cutaneous small-vessel vasculitis).
   (b) Early lesions lack erythema and demonstrate a retiform, branched appearance – represents noninflammatory retiform purpura (usually due to conditions associated with microvascular occlusion).
   (c) Early lesions have prominent erythema and demonstrate a retiform, branched appearance – represents inflammatory retiform purpura (usually due to IgA vasculitis or other subtypes of vasculitis).

(C) Perform history and review of systems to identify factors that may be contributing to purpura, guided by the differential diagnosis of the morphology of the purpura (e.g., preexisting medical conditions or medications that may affect coagulation and hemostasis).

(D) Pursue skin biopsy when the cause of purpura is uncertain.

1. It is imperative to know the age of the lesion chosen for biopsy, since late lesions of noninflammatory retiform purpura (due to microvascular occlusion) develop erythema (inflammation) as a wound healing response to ischemic injury or necrosis. Thus, a late lesion of noninflammatory retiform purpura could appear clinically (and histologically) similar to an early lesion of palpable purpura (e.g., inflammatory hemorrhage due to cutaneous small-vessel vasculitis).
2. Routine histopathology of palpable purpura should be from a lesion no more than 24-48 h old.
3. When the morphology of purpura is concerning for vasculitis, direct immunofluorescence studies should be performed on the skin biopsy (to rule out IgA vasculitis). Direct immunofluorescence in this setting should ideally be performed on an early lesion (less than 24 h old) to ensure the presence of the immune complex deposits.

(E) Targeted laboratory studies can be performed based upon the morphology of the purpura and its accompanying differential diagnosis.
Purpura

**Petechial or Macular (<1cm) (non-palpable)**
- Thrombocytopenia
- Abnormal platelet function
- ↑ intravascular pressure
- Pigmented purpuric dermatosis
- Small vessel vasculitis (a few lesions should be palpable)

**Ecchymotic**
- Coagulation defect
- Hemophilia
- Anticoagulants
- Liver disease
- ↓ Vitamin K

**Inflammatory (erythema present), Round (Some are palpable)**
- Vasculitis (small vessel)
  - Hypersensitivity
  - HSP/IgA vasculitis
  - Cryoglobulinemia (mixed)
  - ANCA-associated
  - Connective tissue disease-associated
  - Lichenoid conditions
  - PLEVA
  - Erythema multiforme
  - If targetoid – IgA vasculitis or erythema multiforme

**Retiform**
- Inflammatory
  - IgA vasculitis
  - ANCA-associated
  - Connective tissue disease-associated
- Non-inflammatory (microvascular occlusion)
  - Cryoglobulinemia (monoclonal)
  - Antiphospholipid Abs
  - Calciphylaxis
  - Warfarin necrosis
  - Heparin necrosis
  - DIC
  - Hypercoaguable state
  - Embolic condition
  - Livedoid vasculopathy
  - Angioinvasive infection
  - Cocaine

Algorithm for approaching the patient with purpura
Erythema Nodosum

Erythema nodosum is an inflammation of the subcutaneous fat (a panniculitis). It is an immunological reaction, elicited by various bacterial, viral and fungal infections, malignant disorders, drugs and by a variety of other causes.

Erythema nodosum is a painful nodular syndrome, most likely of immunologic origin, which involves dermis and subcutaneous tissue.

It is the most frequent clinicopathologic variant of panniculitis.

Some causes of Erythema Nodosum

Infections

Bacteria (e.g. streptococci, tuberculosis, brucellosis, leprosy, yersinia)

Viruses

Mycoplasma

Rickettsia

Chlamydia

Fungi (especially coccidioidomycosis)

Drugs (e.g. sulphonamides, oral contraceptive agents)

Systemic disease (e.g. sarcoidosis, ulcerative colitis, Crohn’s disease, Behçet’s disease)
Erythema Nodosum: large painful dusky plaques on the shins
usually exhibits a sudden onset of symmetrical, erythematous, tender, rounded or oval nodules and raised plaques predominantly located on the extensors of lower extremities, mainly the shins, ankles or knees and more rarely the forearm. Usually the size of the nodules is over 1 cm. At the initial stages, the nodules show a bright red colour evolving toward red or purplish lesions
Erythema nodosum of limbs: symmetrical, erythematous, tender, rounded and oval nodules
Differential diagnoses of EN:

Insect bites

Erysipelas

Erythema induratum
(Nodular vasculitis)

Urticaria

Thrombophlebitis
Malar Erythema

Malar erythema:
is defined as redness symmetrically involving the bilateral cheeks as well as the skin on the bridge of the nose.

Malar erythema:
has many causes, and differentiation is important for diagnosis and management.
Malar rash in a butterfly distribution
Erythema in the butterfly area
Differential Diagnosis:

Genetic disorders:
Certain heritable disorders are associated with photosensitivity and a resultant secondary erythema of the face
.e.g. Bloom’s syndrome or Rothmund-Thompson syndrome

Vitamin deficiency:
Pellagra (deficiency of niacin)

Infections:
Bacterial cellulitis (erysipelas), Many viral infections(including erythema infectiosum, parvovirus B19, primary HIV).

Polymorphous light eruption (PMLE):
Typically, the photosensitivity of polymorphic light eruption tends to be more immediate (e.g., hours) following sun exposure, while classic lupus lesions may take up to 1–2 weeks to develop following sun exposure

Flushing:
Many medications can cause flushing, such as niacin, rare tumors, such as carcinoid, can be associated with flushing

Allergic or photoallergic disorders:

Inflammatory skin disorders:
Acne rosacea can be associated with a malar erythema that is often confused with lupus erythematosus or other related diseases

Lupus erythematosus (SLE)
Dermatomyositis (DM)
Malar Erythema

R/O Hereditary Syndrome (e.g. Bloom’s)

R/O Infection (fever, sudden onset)

Episodic
Associated with heat/burning?

Yes → Flushing disorders

No →

Are Vesicles Primary Lesion?

Yes → Blistering Disorders (e.g. pemphigus)

No →

Centered on Nasolabial Fold?
Yellow, waxy scale?
Preference for eyebrows/scalp?

Yes → Seborrheic Dermatitis

No →

Family History of Atopy?
Involvement of antecubital/popliteal fossae?

Yes → Atopic Dermatitis

No →

Pustules?
Rhinophyma?

Yes → Acne Rosacea

No →

Tissue Disease
- Lupus
- ACLE
- SLE
- Dermatomyositis
- MCTD

Photoallergic or Allergic Contact Dermatitis

PMLE

-Involvement of:
- Cycoids, behind ears
- History consistent
- Outbreak is seasonal
- Reaction to light is immediate

Diagnostic approach to malar erythema
Malar Erythema
Symmetric mid-facial, circumscribed erythema, sparing the nasolabial folds

Malar Erythema
E.g., bilateral flat erythema over malar area, with sparing of nasolabial folds

History & Physical Exam
And laboratory findings e.g., ANA testing

Suspected for rheumatic disease
E.g., acute onset, aggravated by exposure to sunlight; presence of widespread lesions and/or edema, with absence of pustules/papules on exam; significant ANA titer (>1:160)

Inconclusive History and/or Physical Exam

Lesional skin biopsy
3mm biopsy for routine dermatopathology to confirm or rule out rheumatic disease

ANA: anti-nuclear antibody
Livedo Reticularis

**LR** most commonly occurs on the extremities, with the legs usually more affected than the arms

**LR** consisting of a mottled, reticulated vascular pattern resulting from alterations in blood flow through the cutaneous microvasculature system

**LR** may be benign, occurring in healthy individuals without systemic associations, or it can be secondary, occurring in association with underlying disease

**LR** may manifest by any process that reduces arteriole blood flow (vasospasm, hyperviscosity, inflammation, thromboemboli) or venous outflow, leading to accumulation of deoxygenated venous blood
Livedo Reticularis in the legs
Livedo Reticularis
Livedo Reticularis of the lower extremities
livedo Reticularis on the bilateral lower extremities
Differential Diagnosis:

It is important to distinguish LR from livedo racemosa, a distinct entity characterized by a violaceous, irregular net-like pattern that is often annular or polycyclic. 

Livedo racemosa is always secondary to a pathologic process, such as

- SLE,
- antiphospholipid antibody syndrome,
- Sneddon’s syndrome, or
- polycythemia vera,

among others, and classically remains present on rewarming of the skin.

Livedo racemosa is typically asymmetrically distributed and is often more widespread than LR, Involving the extremities, buttocks, and trunk.
LR without systemic associations:

There are three types of LR without systemic associations:

(1) physiologic, which occurs in response to cold and resolves with warming;

(2) primary, in which the appearance and resolution are independent of temperature; and

(3) idiopathic, which is persistent LR without an underlying cause. Both primary and idiopathic LR are diagnoses of exclusion.

LR with systemic associations:

Systemic associations with LR can occur in several broad categories

- Congential,
- Vasospasm,
- Hematologic/hypercoaguability,
- Vasculitis, Autoimmune connective tissue diseases,
- Vessel obstruction,
- Infections,
- Neoplasms,
- Neurologic,
- Medications
LR with Sneddon's syndrome
Calciphylexis

Livedoid vasculopathy

Primary/Idiopathic LR
LR with vasculitis, CTD

Livedo reticularis on clinical exam
(Mottled, reticulated, violaceous pattern)

Resolves with rewarming?
Y  N

Physiologic LR, cutis marmorata
No further work up needed

Evaluate systemic disease based on history and physical.
Consider APS in all patients as well as skin biopsy.

Associated systemic disease identified?
Y  N

Treat systemic disease
Continually present?
Y  N

Idiopathic LR  Primary LR
Telangiectasias

*Telangiectasia* is the visible dilatation of small cutaneous blood vessels. *Mucocutaneous* *Telangiectasias* are dilatation of the capillaries, arterioles, and/or venules of the dermis.
Telangiectasias can occur almost anywhere on the surface of the skin and mucous membranes.
Telangiectasias can be simply a cosmetic nuisance or they can be a sign of underlying disease
Telangiectasia are blanchable. They can be linear, lacy, or matted. If the blood vessels involved are deep (and thus not as compressible from external forces), they can sometimes appear as non-blanching lesions and should still be considered in the differential diagnosis of purpura. Their distribution, configuration, associated signs and symptoms, and the medical history of the patient are all important clues to being able to distinguish between isolated lesions and those which require consideration for underlying systemic pathology.
Differential Diagnosis

**Primary Telangiectasia Syndromes**

Certain hereditary syndromes:
- ataxia telangiectasia,
- Bloom's syndrome,
- xeroderma pigmentosum,
- Sturge-Weber disease,
- Rothmund-Thompson syndrome,
- and Klippel-Trénaunay syndrome

Idiopathic generalized telangiectasia:

*Generalized essential telangiectasia lesions* most commonly begin on the feet, ankles, and distal legs but are characterized by slow extension to other areas. The lesions can be associated with numbness or burning.

- Cutaneous collagenous vasculopathy
- Unilateral nevoid telangiectasia syndrome (UNTS)

**Secondary Telangiectasias**

- Venous hypertension
- Response to many types of trauma
- Induced by certain medications
- Certain systemic or metabolic diseases
- Certain neoplasms
- Certain inflammatory diseases

Sign of underlying rheumatic disease: DM, SLE, SSc
Extensive facial telangiectasia in a man with limited cutaneous SSc
Ulceration

An Ulcer is an area of skin from which the whole of the epidermis and at least the upper part of the dermis has been lost. Ulcers may extend into subcutaneous fat, and heal with scarring.

The causes of Ulceration include trauma, inflammation, vasculopathy, and vasculitis. Inflammation, vasculopathy, and vasculitis may be the result of a connective tissue disease or an adverse effect of drug use.
Connective Tissue Disease (CTD) Ulcerations:

- Behçet’s disease (BD)
- Reactive arthritis (ReA) or Reiter’s syndrome (RS)
- Systemic lupus erythematosus (SLE)
- Systemic sclerosis (SSc)
- Dermatomyositis (DM)
- Rheumatoid arthritis (RA)

Ulceration of the Psoriatic plaques
Ulcers in Vasculitis/Vasculopathy
Behçet’s syndrome

Oral aphthous ulcerations are usually the first and the most frequent manifestation of Behçet’s syndrome.
When the lips are involved they only occur on the mucosal surface.
Oral ulcers of Behçet’s syndrome are usually indistinguishable from ordinary canker sores; however, they are usually multiple and recur more frequently.
Like the former, they also heal without scarring. Minor aphthous ulcers (<10 mm in diameter) are the most common type (~90%);
major or herpetiform ulcers are less frequent.
Bigger or “major” ulcers that can leave scars and impede food passage have occasionally been reported.
Genital ulcerations typically develop on the scrotum (90%) and less frequently on the penis and femoral and perianal regions in men
and on the major labia (70%) followed by the minor labia, vestibulum, and femoral and anal regions in women.
Vaginal and cervical ulcers can, on occasion, also occur.
They heal with scarring in about two thirds of patients when they are large (≥1 cm in diameter).
Urethritis and dysuria are not usually present unless there is secondary infection.
There are mainly three types of skin lesion:

1. **Erythema nodosum–like lesions**
   - are confined to the lower extremities and heal commonly with residual pigmentation as distinct from idiopathic erythema nodosum or that due to other causes.
   - Histologic examination of these lesions shows more vasculitic elements than seen in idiopathic erythema nodosum or other causes.

2. **Superficial thrombophlebitis**
   - may also appear as a nodular skin lesion mimicking erythema nodosum.
   - Superficial thrombophlebitis may be associated with deep vein thrombosis.

3. **The acne-like lesions**
   - are usually indistinguishable from ordinary acne.
   - They occur not only at the usual acne sites but also at uncommon sites such as the legs and arms.
Oral aphthous ulceration in Behcet disease
Genital ulcer in Behcet disease
Genital ulcer in behcet disease
Reiter’s syndrome (reactive arthritis)

The skin lesions (keratoderma blennorrhagicum) are psoriasis-like red scaling plaques, often studded with vesicles and pustules, seen most often on the soles. The toes are red and swollen, and the nails thicken. Psoriasiform plaques may also occur on the penis and scrotum, with redness near the penile meatus. Sometimes nearly the whole skin may be afflicted, and Reiter’s syndrome should be considered in the differential diagnosis of erythroderma.
Keratoderma blennorrhagicum
Circinate balanitis
SLE:

Mucosal lesions may result in ulcers of the mouth, nose, or genital area or produce nasal septal erosions, which occasionally lead to nasal septal perforation. Such lesions have been reported to result from discoid lesions of mucosa or vasculitis.
Mucosal ulcers seen on the hard palate and nasal mucosa
Rheumatoid arthritis (RA)

Pyoderma gangrenosum (PG), Rheumatoid vasculitis, Venous insufficiency, Peripheral Arterial Disease, Peripheral Neuropathy, and Felty’s syndrome are causes of skin ulcers in RA.

The most common location of ulceration is on the lower leg. Leg ulcers in RA patients usually are chronic and occur in patients with seropositive and erosive disease.
Subcutaneous rheumatoid nodule with microinfarcts in a patient with complicated extra-articular RA
Systemic rheumatoid vasculitis. Bilateral foot droop due to mononeuritis multiplex and bilateral lower-extremity vasculitis
Nailfold infarcts in a patient with rheumatoid arthritis
Digital tip and proximal infarcts in a patient with rheumatoid vasculitis
Leukocytoclastic vasculitis with ulceration in a patient with RA
Dermatomyositis (DM)

An ulcer in DM can be the result of calcinosis or vasculopathy. In general, ulcers can indicate one of three CONDITIONS:

1ST, necrotic skin ulceration, especially in non-acral regions and regions without surrounding rash, is considered a predictive factor for the presence of underlying cancer;

2nd, ulceration of Gottron’s papules can occur following DMARD therapy, especially methotrexate or mycophenolate mofetil; and

3rd, patients with melanoma differentiation-associated gene 5 antibodies (MDA5) have a higher incidence of ulcerative cutaneous lesions on the digital pulp and periungual areas, within Gottron’s papules, and over the elbows.
digit pulp ulceration and the lateral erythema in DM
Loss of fingertip pulp, and extrusion of chalky material
Systemic sclerosis (SSc)

The most common type of ulceration in SSc is the Digital ischemic lesion. These ulcerations occur in up to 40% of patients with SSc and can be extremely debilitating due to pain. The lesions come in two forms: Those occurring on the digital pulp and Those occurring overlying extensor joints (such as the interphalangeal joints or metacarpophalangeal joints). The digital pulp lesions usually occur on the digital tips, although they can occur at the hyponychium (the junction of the free edge of the nail plate and the finger tip) or on the lateral tips of the digit.
Digital pits on the fingertip of a patient with scleroderma
Digital gangrene on the fingertips of a patient with scleroderma
Ulcers in Vasculitis/Vasculopathy

can be seen in granulomatous vasculitis like GPA (formerly Wegener’s granulomatosis = WG) and EGPA (formerly Churg–Strauss syndrome = CSS)
Where they tend to occur on the elbows.
In necrotizing inflammation of small to medium arteries in polyarteritis nodosa (PAN), leg ulceration is more common.
Vasculopathic diseases include livedoid vasculopathy, thrombophilic disorders, and cryoglobulinemia
INDIVIDUAL ORGAN SYSTEM INVOLVEMENT IN WEGENER'S GRANULOMATOSIS

Scleritis
Episcleritis
Proptosis
Dacryocystitis
Rhinitis/sinusitis
Septal perforation
'Saddle nose'
Oral and nasal ulcers
Pulmonary infiltrates
Nodules
Pleurisy
Glomerulonephritis
Myalgia
Arthritis/arthralgia
Peripheral neuropathy

CNS

Otitis
Vestibular/auditory
nerve injury

Subglottic stenosis
Endobronchial stenosis

Pericarditis
Endocarditis

ANCA
Usually cytoplasmic
pattern
Anti-PR3 >>> MPO

Skin
Leukocytoclastic
vasculitis
Subcutaneous
nodules
Ulcers
Gangrene

Mass lesions due to WG
- Brain
- Renal
- Orbit
- Lung
- Breast
- Prostate
- Ovary
- Parotid
Oral manifestations of Wegener granulomatitus. Painful tongue ulcer
- Behcet disease
- SLE (painless)
- Scleroderma
- SLE
- DM

**Venous Ulcer**
- Arterial Ulcer
- Neuropathic Ulcer
- Inflammatory Diseases: RP, PG, PAN, CSS and WG
- Cryoglobulinemia
- Thrombophilias

**Common causes of Leg Ulcer**

- Arterial disease
  - Look for abnormal arterial pulse, cold skin with hair loss
- Neuropathy
  - Look for abnormal sensation
- Venous insufficiency
  - Look for lipodermatosclerosis (Hardening of the skin & increased pigmentation)

**Arterial Ulcer**
- Located on distal extremities such as the tips of toes or fingers
- Painful punched out ulcer

**Neuropathic Ulcer**
- Located mainly on pressure areas
- Painful punched out ulcer

**Venous Ulcer**
- Located on medial malleolus
- Painless with irregular border ulcer
Thank You for Attention