

Dermatologic manifestations of connective tissue disorders

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ABSTRACT: Dermatological signs of connective tissue disorders (CTD) are a common presentation to not only dermatologists but more commonly to the general practitioners. CTD encompass a set of diseases whose pathology targets the connective tissue framework of the body mainly the two structural proteins namely elastin and collagen.

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Publication date: January 26th, 2019

A. INTRODUCTION

CTDs can be divided into two main categories of inheritable CTDs and autoimmune CTDs also called systemic autoimmune diseases. In this article, I will majorly be talking about the second type of CTDs.

B. DISCUSSION

1. **Lupus erythematosus (SLE)** is a multisystem autoimmune disorder of connective tissue characterized by autoantibodies that target nuclear antigens (DynaMed Plus 2017). Its main subtype is SLE however skin specific lupus does exist as separate entities.

General Signs: There is no single diagnostic pathological feature for SLE in the skin, but a combination of features that aid in diagnosis (Burns et al. 2016). Among some of the general signs include facial edema, bullous eruptions, chronic urticaria, livedo reticularis, Raynaud's phenomenon, episcleritis and cheilitis to name a few. Well demarcated plaques with adherent scales causing a scarring or non-scarring alopecia is present in about 45% patients at some point of their lives (Uva et al. 2012). Palatal ulcers are most specific for SLE, although all patients with painless or painful ulcers are considered for SLE (Uva et al. 2012). Photosensitivity is another general sign for SLE which was a part of 1997 ACR criteria, however it went out of favor in 2012 SLICC. Small vessel vasculitis is the most common type of vasculitis presenting in SLE patient with typical signs including palpable purpura, urticaria, ulcers, papules and plaques.

Specific Signs: Butterfly or malar rash being the first criterion of ACR with a 96% specificity, is a flat or fixed raised erythema over cheeks and nose sparing nasolabial folds. It is a common specific presentation of acute cutaneous LE (Uva et al. 2012). SCLE is a form of lupus presenting in skin with two classical variants. The annular form having a more dermal involvement, presenting in an urticarial centripetal configuration, whereas the psoriasiform type presents with more epidermal involvement and a centrifugal distribution. Erythema multiforme presenting with SCLE is specific to Rowell's syndrome. Neonatal lupus can also present with the classical skin manifestation of "owl-eye"; confluent erythema around the eyes, with erythematous and violaceous, often scaly patches (Werth 2017). Disc-shaped, erythematous plaques of varying sizes containing areas of follicular hyperkeratosis, which are painful if lifted manually are one of the specific rashes in SLE patients (Uva et al. 2012).

Investigations for establishing Ddx: Many diseases can mimic lupus erythematosus; however, a careful history and investigations can direct a physician towards the right diagnosis. Complete blood count, urinalysis and autoantibody titers are some of the baseline studies to order in a suspected lupus patient along with fulfilling of ACR 1997 criteria or 2012 SLICC criteria. ANA with a sensitivity of 98% (JHLC 2017) combined with anti-dsDNA with a specificity of 98% (Wichainun et al. 2013) can be convincing to favor a lupus diagnosis. Skin or renal biopsy is considered very helpful in establishing a type-specific diagnosis. Rheumatoid arthritis is however an overlap of RA and SLE which is still debatable in whether it is a separate entity or a combination of two diseases in one patient.

2. **Dermatomyositis** is an acquired idiopathic inflammatory myopathy characterized by symmetric proximal muscle weakness and distinctive cutaneous findings.

General Signs: Hyper or hypopigmentation, telangiectasias, skin atrophy, cutaneous vasculitis and skin ulcerations are some of the more general signs of DM (DynaMed 2017).

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Specific Signs: Eyelid skin involvement is one of the most specific cutaneous sign of DM and sometimes even considered pathognomic. The upper eyelids are preferentially affected with an erythema that is lilac (hence called heliotrope rash) in color. However, it is difficult to observe in dark skinned patients (Burns et al. 2016). Another specific sign is erythematous to violaceous macules, patches, or papules on the extensor surfaces of joints in hands, elbows, knees, or ankles called Gottron papules. Patients also present with mechanic's hands denoting non-inflammatory hyperkeratosis occurring on the hands or feet, usually over the radial surfaces of the fingers and the outer border of the feet. Calcinosis cutis (cutaneous calcinosis) is deposition of insoluble calcified material in the skin and subcutaneous tissue. Calcinosis occurs in around 10% of adult DM patients and is more common in patients with longer periods of sustained disease activity, digital ulceration and anti-NXP2 antibodies (Burns et al. 2016). Macular violaceous or poikilodermatous rash is present in patient over shoulders also known as the shawl sign.

Investigations for establishing DDX: Modified Bohan and Peter criteria is used for diagnosis. It includes the presence of heliotrope rash or Gottron papules, plus at least 3 of following are present (Oddis et al. 2005).

- i. progressive, symmetrical proximal muscle weakness in shoulders and hips
- ii. elevated muscle enzyme levels (CK, LD, AST, ALT)
- iii. myopathic pattern on electromyography (EMG)
- iv. muscle biopsy with myofiber degeneration and regeneration, chronic mononuclear inflammatory infiltrate, or perifascicular atrophy

3. **Systemic sclerosis** is a chronic, connective tissue disease of unknown cause that can affect the skin, subcutaneous tissues, and internal organs.

General Signs: Some of the general cutaneous manifestations of SSc include calcinosis, telangiectasias, hair loss on involved skin, ulcerations and pigmentary changes.

Specific Signs: Specific cutaneous manifestations are non-pitting edema and puffiness, which tend to be seen first in the fingers, hands and face. Rapid progression can then occur making the skin taught, indurated, thickened which is then fixed to deeper structures resulting in sclerodactyly. The extension of these changes proximally to the metacarpophalangeal joints is critical to the diagnosis of SSc. Skin sclerosis leads to progressive loss of skin appendages, reduced hair growth, reduced sweating and joint contractures. Nasal 'beaking' and radial furrowing of perioral skin, reduced oral aperture and sclerosis of the frenulum are hallmarks of long-standing disease (Burns et al. 2016).

Investigations for establishing DDX: American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification criteria for diagnosis of SSc states it is definite systemic sclerosis if 1 major criterion or ≥ 2 minor criteria totaling ≥ 9 points (FVD et al. 2013). Criteria do not apply to patients with either skin thickening sparing fingers or scleroderma-like disorder. Major criterion include skin thickening of fingers of both hands extending proximal to metacarpophalangeal joints (9 points) and minor criteria include:

- i. skin thickening of fingers (include only highest score)
 - a) puffy fingers (2 points)
 - b) sclerodactyly distal to metacarpophalangeal joints but proximal to proximal interphalangeal joints (4 points)
- ii. fingertip lesions (include only highest score)
 - a) digital tip ulcers (2 points)
 - b) fingertip pitting scars (3 points)
- iii. telangiectasia (2 points)
- iv. abnormal nail fold capillaries (2 points)
- v. pulmonary arterial hypertension and/or interstitial lung disease (2 points)
- vi. Raynaud phenomenon (3 points)
- vii. presence of any of systemic sclerosis-related autoantibodies (3 points)
 - a) anticentromere
 - b) antitopoisomerase-I (anti-SCL-70)
 - c) anti-RNA polymerase III

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4. **Rheumatoid arthritis** is a systemic inflammatory disease characterized by symmetric, relapsing or chronic destructive synovitis.

General Signs: Erythema and burning sensations preceding joint changes are non-specific cutaneous signs. Skin infections due to impaired immune system along with vitiligo can present in RA patients. RA may also have prominent epitrochlear, axillary, and cervical lymph nodes (JA and D. 2005).

Specific Signs: Subcutaneous (rheumatoid) nodules are present in up to 30% of patients with advanced disease. These are about 1-2 cm in diameter and are usually found at pressure points - elbow, knuckles, ischial spines, occiput, extensor forearm, Achilles tendon. Rheumatoid neutrophilic dermatitis presents with classical lesions that are papulo-nodules and/or plaques distributed on the extensor surfaces of extremities particularly the hands and forearms as well as the neck and trunk (Sharma and Albert 2015).

Investigations for establishing DDX: Initial testing in patients with suspected RA includes rheumatoid factor (RF), anticyclic citrullinated peptide (anti-CCP) antibodies, complete blood count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function tests, x-rays, MRI, US or aspiration of the joints involved.

- C. **CONCLUSION:** Connective tissue diseases present a diagnostic challenge to dermatologists and general physicians given the wide range of cutaneous manifestations. It is of imminent importance for the physicians to be able to recognize and pick some of the earliest signs in these connective tissue diseases, which in most cases are cutaneous manifestations. Since most of the CTDs are diagnosed by fulfillment of specific criteria that encompass different organ systems, use of clinicopathologic correlation of symptoms, signs, immunology and histology to confirm the diagnosis and differentiate between them is of key importance.

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