

Rheumatic manifestations of skin disease

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Purpose of review

There is an increasing interest in improving the understanding of pathophysiology, outcome measures, and therapies of rheumatic skin disease. Increasingly, studies are using the skin as a primary endpoint for evaluating therapies. This will review the current state of the art for the most common rheumatic skin diseases.

Recent findings

A number of medications, including biologics such as tumor necrosis factor α and interferon, have been associated with onset of cutaneous lupus. The cutaneous lupus erythematosus area and severity index has been further validated and utilized in a number of studies. Smoking continues to be associated both with presence and refractoriness of cutaneous lupus erythematosus to therapy. There are several tools now available for evaluating the skin disease of dermatomyositis, but there is a need for new effective therapies. Measurement of skin disease in scleroderma continues to be a challenge, and there is a need for more effective therapies. Several studies show efficacy of intravenous iloprost for severe Raynaud's and skin ulcers, and of bosentan for digital ulcers.

Summary

The present review covers new outcome measures, treatments, and unusual manifestations of cutaneous lupus, dermatomyositis, scleroderma, and rheumatoid arthritis. There have been a number of new studies related to validation of disease activity measures, as well as their use in evaluation of new therapies for these conditions. Validated outcome measures are required to perform meaningful studies, and will facilitate organized epidemiologic, quality of life, and therapeutic studies.

Keywords

cutaneous lupus erythematosus, dermatomyositis, rheumatoid arthritis, scleroderma

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Introduction

Recent advances in the understanding of cutaneous findings in cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE), dermatomyositis, systemic sclerosis (SSc), and rheumatoid arthritis (RA) in terms of clinical evaluation, triggers of disease, outcome measures, systematic clinical studies, and treatment will be discussed.

CLE includes lupus specific and lupus nonspecific skin lesions. Lupus specific skin lesions include chronic CLE, subacute CLE, and acute CLE [1,2]. Chronic CLE includes localized, generalized, and hypertrophic lupus erythematosus, lupus panniculitis, lupus tumidus, and lupus pernio. The criteria for SLE include four dermatologic criteria, some of which are potentially overlapping. Patients can meet four criteria for SLE based solely on dermatologic findings, and some of these patients are not systemically ill [3]. These criteria include malar rash, photosensitivity, discoid lesions, and oral ulcers. Patients with lupus nonspecific skin lesions are more frequently

systemically ill with SLE relative to patients with lupus specific skin lesions [4]. Medications are a frequent trigger of subacute cutaneous lupus erythematosus (SCLE), and the list of drugs that are associated continues to expand. There have not been many systematic studies of CLE [5]. With the development of the Cutaneous Lupus Area and Severity Index (CLASI), a validated outcome measure for CLE, it is hoped that more systematic epidemiologic and therapeutic trials will be performed [6,7].

Skin lesions in dermatomyositis are frequently clinically distinctive, with pathognomonic lesions including Gottron's papules with lesions targeting over joints, and characteristic lesions including a heliotrope, peri-ungual telangiectasias, dystrophic cuticles, and photo-distributed violaceous erythema. Biopsy of the skin for routine histology frequently looks identical in cutaneous lupus and dermatomyositis.

Cutaneous findings are manifestations important in the classification SSc. Raynaud's phenomenon may precede the onset of SSc by years, especially in localized

cutaneous SSc (lcSSc). Cutaneous sclerosis typically commences on the distal extremities. Although gradual and often limited to these areas in lcSSc, in diffuse cutaneous SSc (dcSSc), the sclerosis is often preceded by nonpitting edema, rapidly progressive, and more diffuse. Telangiectases are prominent especially on the face. The skin is dry and often pruritic. Areas of hyperpigmentation and hypopigmentation may be seen. Painful digital ulcers arise as a consequence of ischemia.

Cutaneous manifestations of RA include rheumatoid nodules, rheumatoid vasculitis, and granulomatous dermatoses. Patients with RA are at risk of developing psoriasiform cutaneous adverse reactions to tumor necrosis factor α (TNF α) inhibitors.

Cutaneous lupus erythematosus

Patients can have skin findings of CLE alone or have CLE associated with underlying systemic disease.

Cutaneous findings in cutaneous lupus erythematosus

There have been several recent reports about papulomucinous lupus erythematosus, otherwise termed lupus tumidus, as a subset of chronic cutaneous lupus. Patients with this variant tend to have negative antinuclear antibodies (ANA), increased susceptibility to lesion induction with ultraviolet light, minimal changes at the dermal–epidermal junction on skin biopsy, and they frequently do not have other manifestations of SLE. Rarely these patients have concurrently other forms of CLE, thus suggesting that tumid lupus erythematosus fits, despite many differences from other forms of CLE, in the spectrum of chronic CLE. There is an ongoing debate about the exact categorization of lupus tumidus [8[•]].

Descriptions of the clinical appearance of cutaneous lupus, including those resembling acne and comedones in discoid lupus, emphasize the heterogeneous clinical presentations of CLE [9[•]].

Two families have a well defined mutation of three prime repair exonuclease 1 (TREX1). The mutant TREX1 enzyme diminishes TREX1 function and studies suggest a role for TREX1 in double-stranded DNA (dsDNA) degradation to prevent immune activation [10^{••}].

Oral lesions in lupus patients can be confusing. The clinical differential diagnosis of oral lupus lesions depends on whether the lesions are keratotic, ulcerated, lip lesions, erythematosus purpuric macules, or bullous [11^{••}]. For instance, ulcerated discoid lesions have a differential that includes aphtha, erosive lichen planus, traumatic ulcers, deep fungal infection, Langerhans cells histiocytosis, and squamous cell carcinoma. Biopsy of oral ulcers due to lupus show pathologic changes identical to

those seen in the skin, and typically do not indicate vasculitis.

Triggers

There are a number of triggers of cutaneous lupus. Several recent studies have examined the low but measurable output of ultraviolet B (UVB) from compact fluorescent lights, suggesting that these should be covered in the setting of lupus patients [12[•],13[•]]. Others have reported new medications or reviews of medications associated with subacute cutaneous lupus, including capecitabine and sertraline [14[•]]. Anti-TNF medications continue to be reported in association with subacute cutaneous lupus, as well as injection-site reactions from interferon- β (IFN β) that show lupus on biopsy.

Outcome measures

The absence of validated outcome measures for cutaneous lupus has hampered the ability to do clinical trials or perform careful clinical cohort studies. Recent studies have expanded the initial validation of the CLASI, examining the responsiveness of the CLASI in a trial, and extending validation to rheumatology [15^{••},16^{••}]. Recognition of the need for core sets of data to systematically evaluate lupus populations have been developed [17[•]].

Epidemiology/organized studies

One study examined the incidence of cutaneous lupus over a 40-year period in Olmsted County, Minnesota, and found an incidence rate of CLE of 4.3, with 19% progressing to SLE over a 20-year period [18^{••}]. The development of a web-based database for cutaneous lupus has allowed systematic characterization of the disease severity and quality of life of cutaneous lupus patients examined in an academic center. The most therapeutically resistant patients are more likely to be smokers, confirming this risk factor for refractory disease [19[•]]. One study also confirmed that smoking is a risk factor for developing CLE [20[•]]. A systematic study of anti-Ro/SSA-positive patients with skin manifestations demonstrated that these patients do develop new autoimmune diseases and are potentially at risk of drug-induced SCLE [21[•]]. Pediatric discoid lupus erythematosus (DLE) is rarer, but potentially more frequently associated with SLE, particularly when generalized [22[•]].

Treatment of cutaneous lupus erythematosus

Sunscreens and sun avoidance are important aspects of treatment and prevention in CLE patients. As a result, patients frequently have low vitamin D levels and should be supplemented [23^{••}].

There have been extraordinarily few controlled trials for cutaneous lupus. Thus, most therapy is guided by case series, case reports, and expert opinion. Topical

calcineurin inhibitors are used as adjunctive therapy [24[•]]. Systemic therapy for disease that is scarring, unresponsive to topical therapy, or widespread involves hydroxychloroquine at a dose of less than 6.5 mg/kg/day. For therapeutically resistant patients, there is sometimes a benefit by adding quinaquine at a dose of 50–100 mg/day. Another study of lupus erythematosus tumidus demonstrated that 61% of patients had a complete or near complete response to antimalarials, with smokers having higher initial clinical score and being less responsive to treatment [25[•]]. A preliminary study of two refractory CLE patients suggested that one of the patients had some improvement with lenalidomide, although its use in SLE may be problematic because of risk of immune stimulation [26[•]]. One open prospective study suggested that the pulsed dye laser can be effective in treating DLE [27[•]].

Thalidomide is an effective therapy for refractory CLE. However, there is a high incidence of sensory axonal neuropathy, the total dose of thalidomide that can cause this is relatively low, and recovery in one study occurred in 25% based on sural nerve sensory action potentials (SAP) [28[•]].

Dermatomyositis

Dermatomyositis can involve only the skin (amyopathic) or have only mild muscle findings on lab testing without clinical symptoms or signs (hypomyopathic). Pathognomonic findings include Gottron's papules and Gottron's sign. Characteristic findings include a heliotrope, peri-ungual telangiectasias, dystrophic cuticles, and photo-distributed violaceous erythema.

Diagnosis

Skin biopsies should be obtained in patients in whom dermatomyositis is in the differential, largely to determine whether the patient has an autoimmune skin disease. There is still confusion about how to diagnose amyopathic dermatomyositis, as these patients by definition do not have muscle disease and thus cannot fulfill the current criteria for dermatomyositis. Skin biopsy will not differentiate CLE from dermatomyositis, and thus clinical–pathological correlation is the key to making the diagnosis [29[•]].

Triggers

There are a number of potential drug triggers of dermatomyositis, including hydroxyurea, IFN β 1a, and TNF blockers [30[•]–33[•]].

Outcome measures

There have been few studies of dermatomyositis related to the skin. Hopefully, the development of validated tools will facilitate this process [34[•],35[•]].

Systemic sclerosis

Cutaneous changes are common, early manifestations of SSc, important in the classification of this heterogeneous disease. The two major subtypes, limited cutaneous SSc (lcSSc) and dcSSc, are distinguished in part by the acuity and extent of cutaneous findings.

Cutaneous outcome measures

Skin sclerosis is one of the most common endpoints used in studying SSc; however, the relationship between sclerosis and disease morbidity and mortality is complex. A number of studies have linked the course and severity of cutaneous sclerosis with overall disease prognosis [36,37]. Rapid worsening of cutaneous sclerosis has been associated with renal crisis and reduced survival among patients with antitopoisomerase antibodies [38]. More recently; however, Shand *et al.* [39] applied a latent linear trajectory model to determine whether changes in modified Rodnan skin score (mRSS) are directly related to disease morbidity and mortality among dsSSc patients. Whereas the highest mortality occurred among patients with the greatest baseline mRSS who had minimal improvement over time, those with high or low baseline mRSS who subsequently improved had as many or more systemic complications as those in the highest mortality group. An analysis of 1200 patients enrolled in the German Systemic Sclerosis Network, revealed that patients with higher mRSS had a greater frequency of dysphagia, reflux, pulmonary fibrosis, digital ulcers, and joint contractures, but mRSS had no relationship with the frequency of any other systemic manifestation [40^{••}]. Complicating matters further is the tendency of cutaneous sclerosis to improve spontaneously over time in some patients and the use of disease modifying agents that may have altered the severity of skin findings by patients in these studies.

The measurement of sclerosis also poses challenges. Although the fully validated mRSS has been considered the gold standard evaluative tool, its responsiveness has been somewhat modest in several trials, and it has been argued that it may not be sensitive enough to detect small but clinically relevant changes [41]. Additionally, the reliable administration of the mRSS requires training and experience [42]. Several other tools used include ultrasound measurement of dermal thickness, durometer, elastometer, twistometer, cutometer, and plicometer, but limitations to their use include lack of responsiveness in clinical trials, difficulty to administer or learn, poor reproducibility, or cost [43]. Recent recommendations from the Scleroderma Clinical Trial Consortium include the use of mRSS, durometry, and a visual analog scale in clinical trials of SSc [44].

Treatments

Therapies aimed at reducing cutaneous sclerosis are limited. Topical corticosteroids and calcineurin inhibitors

are minimally beneficial as they fail to penetrate into affected dermal tissue. Phototherapy with wavelengths in the UVA spectrum has been shown to soften skin and reduce dermal thickness in sclerosing disorders including SSc [45,46,47]. Systemic immunosuppressive agents including corticosteroids, methotrexate, cyclophosphamide, and cyclosporine have been used with varying success to improve sclerosis. The role of D-penicillamine has been controversial, with benefits reported in open and retrospective trials [36,48] but with no difference demonstrated in a double-blind randomized controlled trial comparing high and low dosages [49]. A recent trial of mycophenolate mofetil combined with intravenous and oral corticosteroids demonstrated improvement in mRSS [50]. Conflicting results have been reported in two recent small trials of the anti-CD20 molecule, rituximab, with improvement in mRSS reported in one study [51], but not the other [52]. A lack of efficacy and an increased morbidity and/or mortality have been reported from trials of recombinant relaxin [53] and a recombinant anti-tissue growth factor $\beta 1$ (TGF $\beta 1$) antibody [54].

In addition to sclerosis, vascular disorder contributes to cutaneous manifestations of scleroderma including Raynaud's phenomenon and digital ulceration. Treatment remains challenging. Intravenous iloprost is approved for the treatment of severe Raynaud's phenomenon with ulcerations, and a recent open-label randomized trial demonstrated equal efficacy of low and high dose iloprost [55]. In Europe, the endothelin receptor antagonist, bosentan, has been approved for prevention of digital ulcers. To better predict those at risk for digital ulcers, Sebastiani *et al.* [56] utilized nailfold videocapillaroscopic data to create a mathematical model capable of predicting digital ulcers with a sensitivity of 85.9% and specificity of 94.3%.

Insights into the pathogenesis of SSc have led to potential novel therapeutics. Inhibition of histone deacetylase-7 *in vitro* led to decreased type I and III collagen synthesis; this enzyme may be a potential therapeutic target in SSc [57]. The stimulatory effects of TGF β on extracellular matrix synthesis are mediated by connective TGF (CTGF). Administration of an anti-CTGF antibody inhibited TGF β -induced fibrosis in a murine model of fibrosis [58]. Finally, closer yet to bedside are tyrosine kinase inhibitors such as imatinib. By inhibiting platelet-derived growth factor receptor (PDGFR) signaling, they reduce cutaneous and systemic fibrosis as demonstrated by in-vitro, animal, and human data [59,60]. Clinical trials of imatinib for SSc are ongoing.

Rheumatoid arthritis

The pathomechanisms of the cutaneous manifestations of RA including rheumatoid nodules, granulomatous

dermatoses, and rheumatoid vasculitis are unknown; however, immune complex deposition and/or small vessel vasculitis are likely important.

Rheumatoid nodules

Rheumatoid nodules are the most common extra-articular manifestation of RA and occur in 20–30% of affected individuals. They are more common in men and in those with rheumatoid factor seropositivity. They appear as flesh-colored, firm, subcutaneous nodules that range in size from millimeters to several centimeters. They are usually painless and often occur over extensor surfaces or at sites of repetitive stress. Nodules may shrink, persist, or worsen with RA treatment. Accelerated nodulosis, characterized by the abrupt onset or worsening of rheumatoid nodules, has been described following therapy with leflunomide [61], methotrexate, TNF-inhibitors, and with an aromatase inhibitor for breast cancer in a patient with RA [62].

Rheumatoid vasculitis

The skin is involved in 75–89% of patients with rheumatoid vasculitis, often as the presenting sign of the condition [63]. Purpura, livedo reticularis, atrophie blanche, and ulcers are cutaneous signs of rheumatoid vasculitis. It is associated with longstanding, erosive, seropositive disease, and is more frequent in those with antibodies to citrullinated peptides [64]. TNF-inhibitor therapy has been associated both with onset and improvement of rheumatoid vasculitis [64,65]. Treatment with argatroban, an antithrombin agent, in a patient with antiphosphatidylserine–prothrombin complex antibodies led to resolution of ulcers refractory to immunosuppressive therapy [66].

Granulomatous dermatitis

Interstitial granulomatous dermatitis (IGD) and palisaded neutrophilic and granulomatous dermatitis (PNGD) are eruptions associated with autoimmune diseases including RA. These eruptions represent reaction patterns related to cutaneous immune complex deposition [67]. The polymorphous eruption of IGD favors the trunk, thighs, and axillae in a symmetric fashion and is characterized by erythematous, indurated, linear bands, papules, nodules, or annular plaques. PNGD is characterized by symmetric papules and nodules on the extremities. Spontaneous resolution is common, but treatments including NSAIDs, prednisone, dapsone, colchicine, oral tacrolimus [68], and TNF-inhibitors [69] have been reported. TNF-inhibitors have also been linked to onset of the eruption [70,71].

Psoriasisiform eruptions related to tumor necrosis factor α inhibitor therapies

Patients treated with TNF α inhibitors may develop an eruption that is clinically and histologically indistinguishable from psoriasis. This can occur in those receiving these agents for any condition; although those with RA

appear to be at greatest risk. The eruption typically clears with drug cessation, and may or may not recur during treatment with other drugs of this class [72–74].

Conclusion

Skin manifestations are often prominent or at times sole features of lupus erythematosus, dermatomyositis, SSc, and RA. The easy observability and accessibility of the skin for study has and will continue to enhance our understanding of the pathogenesis of these systemic diseases. The development of validated outcome measures is imperative for reliably objectifying the cutaneous manifestations of these diseases and their response to therapeutic interventions. Patient databases and multidisciplinary collaboration will enable the performance of larger and more meaningful clinical trials.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 103–104).

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