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Skin in rheumatic disease

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- Skin is involved frequently in rheumatic diseases.
- Skin manifestations can be hallmark features in some rheumatic diseases, especially lupus erythematosus, dermatomyositis, and systemic sclerosis.
- Skin changes in rheumatic diseases are specific when characterized by a distinct clinical and histopathologic picture.
- Nonspecific skin changes occur in a variety of diseases but not exclusively in a distinct rheumatic disorder.
- Skin involvement can alert the clinician to a different course, therapeutic approach, and prognostic outcome in a patient with rheumatic disease.

INTRODUCTION

Skin changes occur in a variety of rheumatic diseases and are of particular relevance for clinicians dealing with such diseases for several reasons. First, skin can be the initial site of involvement in a rheumatic disease, thereby providing the physician with important clues to the correct diagnosis. Second, skin involvement in a rheumatic disease may serve as an easy-to-access indicator of both systemic involvement and prognostic outcome of the disorder. Third, because of the important psychosocial function of the skin, physicians need to be fully aware of the impact that chronic and often disfiguring skin changes may have on the quality of life of a patient with rheumatic disease. Fourth, skin changes may be induced *de novo* in a patient with rheumatic disease after the initiation of systemic therapy. The rapid advancement in the field of biologics and targeted therapies (e.g., tyrosine kinase inhibitors) for the treatment of rheumatic diseases requires pharmacovigilance for the skin as a frequent site of adverse effects. Finally, elucidation of the pathobiology of skin manifestations will undoubtedly provide important insight into the pathogenesis of rheumatic disorders and allow novel therapeutic approaches.

This chapter describes skin manifestations of the major systemic connective tissue disorders: systemic lupus erythematosus (SLE), dermatomyositis (DM), systemic sclerosis (SSc), and Sjögren syndrome (SjS). This is followed by a heterogeneous group of other systemic rheumatic diseases: rheumatoid arthritis (RA), psoriatic arthritis (PsA), systemic-onset juvenile rheumatoid arthritis (SOJRA), and relapsing polychondritis (RP). It is beyond the scope of this chapter to describe all rheumatic diseases with skin manifestations. The chapter starts with a section describing the general approach to patients with skin manifestations of a rheumatic disease.

APPROACH TO THE PATIENT

To assess skin involvement of a patient with rheumatic disease, a full-body inspection, including the scalp, anogenital area, and mucous membranes, should always be performed because the skin manifestations of rheumatic diseases often have a predilection for distinct body sites that can otherwise easily be overlooked. Examples of such situations are mucosal lesions in the oral cavity of patients with lupus erythematosus (LE) or intertriginous involvement by psoriasis in patients with arthritis. Inspection of all skin appendages (i.e., scalp hair and nails) is also an integral part of any routine dermatologic inspection. Notably, nail changes can be an important indicator of PsA, whereas scarring alopecia may be a troublesome skin manifestation of LE. Full-body inspection also enables the physician to determine the precise extent and severity of skin involvement in a rheumatic disease.

Accordingly, scores to assess the extent and severity of skin involvement have been developed for LE, SSc, and psoriasis and can be used to precisely monitor the efficacy of any treatment.

The skin changes as seen in systemic rheumatic diseases are said to be *specific* when they display characteristic and sometimes even pathognomonic features along with a typical histopathology encountered only in a distinct rheumatic disease. On the other hand, cutaneous manifestations can be *nonspecific* and occur in a diversity of rheumatic and nonrheumatic systemic diseases. It is also well established that some skin diseases have an increased incidence in patients with selected systemic rheumatic diseases. These dermatoses are best referred to as *associated skin diseases*. In some cases only the combination of specific and nonspecific skin changes in the presence of an associated skin disorder may establish the final diagnosis of a rheumatic disease. Description of the skin lesions encountered in patients with rheumatic diseases requires precise terminology. [Box 33.1](#) lists and explains common dermatologic terms encountered in this chapter.

A minimally invasive procedure (e.g., skin biopsy; see Chapter 32) is often helpful to precisely determine the nature of a skin lesion in patients with rheumatic disease. Although most skin lesions can easily be assessed by punch biopsies, involvement of deeper layers of the skin, such as in lupus panniculitis, requires deep incisional biopsies to not miss the diagnosis. Routine processing of skin biopsy specimens with paraformaldehyde fixation is usually sufficient to establish the diagnosis by histopathology, whereas cryopreservation is needed to visualize immunoglobulin deposits by specific staining. It is important to note that immunosuppressive or immunomodulatory treatment (systemic and topical) can severely mask the natural histopathologic picture of a specific skin lesion. Because of the turnover rate of human epidermis, cessation of any such treatment for at least 3 weeks is recommended before skin biopsy.

MAJOR SYSTEMIC CONNECTIVE TISSUE DISORDERS

Systemic lupus erythematosus

Key dermatologic signs of SLE include photosensitivity; malar dermatitis; discoid rash; other forms of specific cutaneous lupus erythematosus (CLE), localized or generalized, involving the epidermis, dermis, or subcutaneous fat of the skin; and oral ulcerations.

Skin involvement is the second most common manifestation of SLE after arthralgias. In approximately 25% of patients with SLE, skin is the first site of disease involvement. According to an Italian study, skin lesions develop in more than 75% of all patients with SLE during the course of their disease.¹ However, patients with SLE may have no signs of skin involvement, a condition called “*lupus sine lupo*.”

Classification of the skin manifestations of LE (CLE) is complex and may be a challenge, especially for novice and nondermatologist physicians. Precise description of the type of CLE is of importance because different subtypes have a different predisposition to systemic involvement of LE. Notably, different subtypes of CLE can occur both in patients with SLE and in patients with no systemic involvement.

The most widely accepted classification of LE was developed by Gilliam and Sontheimer.² It divides LE-specific skin disease into three major clinical subtypes according to their disease acuity: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) ([Box 33.2](#)).³ These subtypes are further specified according to the extent of their skin involvement (local vs. generalized), morphology, and localization of the inflammatory infiltrate in the skin (e.g., LE panniculitis indicating LE-specific infiltration of adipose tissue). It

BOX 33.1 FREQUENTLY USED DERMATOLOGIC TERMS

Erosion—a superficial tangential defect of the epidermis

Erythema—generalized erythema of the skin

Koebner phenomenon—induction of specific skin lesions by nonspecific trauma such as scratching

Macule—a flat localized discoloration of the skin; when the discoloration is red, it is called *erythema*.

Onychodystrophy—disturbed growth of the nail plate

Onycholysis—separation of the nail plate from the nail bed (hyponychium)

Papule/nodule/plaque—a raised, localized, solid skin lesion; when the raised lesion has spread horizontally, it is referred to as a *plaque*.

Pathergy phenomenon—induction of specific skin lesions by intracutaneous injection of sterile NaCl or as a result of venipuncture.

Poikiloderma—a combination of hyperpigmentation, hypopigmentation, telangiectasia, and skin atrophy

Purpura/petechia—localized intradermal hemorrhage; when less than 3 mm in diameter, it is called *petechial*.

Pustule—a vesicle filled with pus

Sclerosis—induration of the skin

Squama—localized area of abnormal shedding of the corneal layer of the epidermis

Ulcer—a substantial defect of the epidermis and deeper layers of the skin (dermis, subcutaneous tissue); it inevitably leads to scar formation.

Urtica/wheal—a transient raised skin lesion attributable to dermal edema; the center of the lesion is pale and the borders are erythematous.

Vesicle/bulla—a localized, raised lesion of the skin filled with exudate, either serous or hemorrhagic fluid; when larger than 0.5 cm in diameter, a vesicle is called a *bulla*.



Fig. 33.1 Generalized acute cutaneous lupus erythematosus. Note the typical distribution with sparing of the knuckles.



Fig. 33.2 Subacute lupus erythematosus (annular subtype). Note the characteristic localization on the upper part of the trunk (V shape).

BOX 33.2 CLASSIFICATION OF LUPUS ERYTHEMATOSUS-SPECIFIC SKIN LESIONS

- A. Acute cutaneous lupus erythematosus (ACLE)
 1. Localized ACLE
 2. Generalized ACLE
 3. Toxic epidermal necrolysis–like ACLE
- B. Subacute cutaneous lupus erythematosus (SCLE)
 1. Annular
 2. Papulosquamous
- C. Chronic cutaneous lupus erythematosus (CCLE)
 1. Discoid lupus erythematosus (DLE)
 - a. Localized
 - b. Generalized
 2. Hypertrophic/verrucous lupus erythematosus
 3. Lupus erythematosus tumidus
 4. Lupus panniculitis/profundus
 5. Chilblain lupus erythematosus
 6. DLE–lichen planus overlap

Modified from Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. *Best Pract Res Clin Rheumatol* 2004;18:429-62.

is important to note that in patients with SLE (as in patients with CLE only), different forms of LE-specific skin lesions can be present simultaneously (e.g., a butterfly rash as a manifestation of localized ACLE plus chilblain LE as a variant of CCLE).

The hallmark skin lesion of ACLE in patients with SLE is malar dermatitis, which is a reddish maculopapular eruption in a characteristic butterfly distribution on the face (see Fig. 126.1). In most cases patients recall induction or exacerbation of the rash by exposure to ultraviolet (UV) light, thus indicating that photosensitivity is an important diagnostic clue and pathogenetic component. Lesions tend to be transient, last from several hours to weeks, and heal without scarring. Occasionally, poikiloderma (characterized by dyspigmentation, prominent blood vessels, and thinning of the skin) can occur. When generalized, ACLE can involve the trunk with accentuation of the UV-exposed areas but may be localized elsewhere, including the hands, where the knuckles are typically spared (Fig. 33.1). A recently recognized life-threatening variant is toxic epidermal necrolysis–like ACLE. This condition may be regarded as a fulminant form of generalized ACLE in which a massive epidermal injury occurs, possibly because of severe alterations in the dermoepidermal junction and subsequent apoptosis. Another variant is

Rowell syndrome, which was originally described as an erythema multiforme–like eruption in patients with disseminated LE (DLE) and positive anti-Ro/La antibodies. However, subsequent reports and our own observations suggest that similar skin lesions can also develop in patients with SLE and SCLE, as well as in the presence or absence of anti-Ro/La antibodies. Oral lesions are a common mucocutaneous manifestation in patients with SLE and are part of the American College of Rheumatology (ACR) criteria. Typically, they consist of painful aphthoid lesions and ulcerations, especially on the lips and buccal and palatal mucosa, but they may be localized elsewhere in the oral cavity. Some palatal lesions may be asymptomatic.

Patients with clinical features of SCLE usually have circulating anti-Ro and anti-La antibodies and the HLA-B8 and HLA-DR3 haplotype. Notably, SCLE may be induced by drugs, especially antihypertensives and antifungals. This drug-induced type of SCLE does not appear to differ clinically, histopathologically, or immunologically from idiopathic SCLE.⁴ Two variants have been identified: an annular (or arcuate) variant consisting of slightly raised erythema with central clearing and a papulosquamous variant consisting of psoriasis-like or eczematous-like lesions, both typically located on UV-exposed skin, including the lateral aspects of the face, the V of the neck (often with sparing of the area under the chin), the upper ventral and dorsal part of the trunk (Fig. 33.2), and the dorsolateral aspects of the forearms. SCLE lesions never lead to scarring, but hypopigmentation or depigmentation as a result of postinflammatory destruction of epidermal melanocytes is a common complication during the healing process of these skin lesions (Fig. 33.3), especially in patients with darker skin phenotypes. A substantial proportion of patients with SCLE exhibit mild systemic symptoms, especially arthralgias and musculoskeletal complaints. Data from several studies indicate that the proportion of patients with SCLE fulfilling four or more ACR criteria for SLE ranges from 30% to 62%. Therefore,



Fig. 33.3 Residual vitiligo-like skin lesions in a patient with subacute cutaneous lupus erythematosus.



Fig. 33.4 Lupus erythematosus tumidus. Note urticarial plaques on the face and neck.

patients with SLCE need to be monitored closely during the course of their disease to exclude transition into SLE.

The prototypic skin lesion of the classic form of CCLE, also known as discoid CLE, is an erythematous discoid plaque that becomes hyperkeratotic and eventually leads to atrophy and scarring. This subtype of CLE occurs more often in black than in white individuals.⁵ Dyspigmentation, including hypopigmentation and hyperpigmentation, is common. Discoid lesions have a predilection for the face, ears, and neck but may be widespread without a clear-cut relationship to UV exposure. Disfigurement can be a serious problem, especially in patients with facial involvement. Mucosal membranes, including the lips, mucosal surfaces of the mouth, nasal membranes, conjunctivae, and genital mucosa, may also be involved with characteristic discoid lesions resembling leukoplakia. Although DLE is considered primarily a form of CLE without systemic involvement, patients with SLE may have classic DLE lesions. Long-term follow-up of patients with DLE is also necessary because according to retrospective analysis of a number of studies, SLE will develop in 5% to 10% in the course of the disease.

As outlined in Box 33.2, several other subtypes of CCLE can occur in patients with SLE and nonsystemic LE. In hypertrophic/verruccous CCLE, epidermal hyperkeratosis is prominent and results in lesions with thick scaling. LE tumidus is a rare variant of CLE characterized by photosensitive erythematous, sometimes urticarial plaques and nodules without epidermal hyperkeratosis or follicular plugging.⁶ Lesions are usually located on the face, upper part of the trunk, and extremities (Fig. 33.4). The majority of patients with LE tumidus do not have antinuclear antibodies, and diagnosis relies mainly on the clinical and histomorphologic picture. Because the course and prognosis of LE tumidus are generally more favorable than in other subtypes of CLE, it was suggested that this CLE subtype be labeled “intermittent subtype of CLE.”^{6,7} In contrast, LE panniculitis is a very



Fig. 33.5 Chilblain lupus erythematosus of the toes.

chronic CLE subtype consisting of intense inflammation within the adipose tissue of the skin that results in indurated plaques and lipoatrophy. Lesions are commonly seen on the face, proximal parts of the extremities, upper part of the trunk, and buttocks and can be disfiguring. When the overlying dermis and epidermis are involved in LE panniculitis, it is called *LE profunda*. As shown in a retrospective study of 40 patients with this CCLE variant, few patients (10%) fulfill the ACR criteria for SLE.⁸ Another variant of CCLE is chilblain LE, which denotes pernio-like skin lesions (i.e., red to violaceous plaques located on the distal parts of the extremities—fingertips, toes, and occasionally other parts of the body) that are typically induced and aggravated by exposure to cold (Fig. 33.5). These patients should be monitored carefully because SLE will develop in up to 24% of them.⁹

In the past, SLE disease activity, including some dermatologic criteria, has been assessed by various outcome measurements and scores. Recently, a “Revised CLE Disease Area and Severity Index (RCLASI)” has been introduced.¹⁰ This modified outcome instrument now includes the various CLE subtypes, as well as disease activity parameters (e.g., edema, scaling, hypertrophy, or dyspigmentation). The score had an intraclass correlation coefficient for an interrater reliability of 0.89 for the activity score and 0.79 for the damage score. The RCLASI may be used especially in clinical trials of patients with CLE to precisely assess skin involvement.

Histopathologic examination of a biopsy specimen from specific skin lesions may facilitate the correct diagnosis in a patient with LE. However, it should be noted that proper classification of the various CLE subtypes is based primarily on macroscopic skin morphology whereas the diagnosis of SLE relies on the overall clinical picture, including possible other organ manifestations and laboratory or serologic analysis. In acute forms of cutaneous involvement, LE-specific histologic changes can be subtle. ACLE lesions show vacuolar degeneration of the dermoepidermal junction, dead keratinocytes (“Civatte bodies”), and a sparse lymphohistiocytic infiltrate of the upper dermis. Dermal blood vessels are dilated with extravasation of erythrocytes. In SCLE, these findings are often associated with epidermal atrophy. The lymphohistiocytic infiltrate is located in the upper dermis with an interface and perivascular pattern. Classic DLE lesions have additional epidermal hyperkeratosis and thickening of the dermoepidermal and follicular basement membranes. The lymphohistiocytic infiltrate is often prominent and involves hair follicles, which may also show hyperkeratotic plugging. Mucin may be deposited in the dermis. Deeper forms of CCLE are characterized by a lymphohistiocytic infiltrate situated in the lower dermis, often with mucin deposits (LE tumidus), whereas in lupus panniculitis, the infiltrate is located primarily in the subcutaneous fat tissue. Direct immunofluorescence (DIF) can be used to assess the presence of immunoglobulin (IgG, IgM, and rarely IgA) and complement (C3) along the dermoepidermal junction in frozen sections of CLE lesions. In patients with SLE, this test (“lupus band test”) is typically positive even in nonlesional, sun-protected skin. However, DIF studies currently provide little benefit to the overall diagnosis and classification of LE and may be used only to discriminate between CLE and skin diseases with similar histopathologic findings.

The differential diagnosis of ACLE lesions includes erythema solare (sunburn), photoallergic and phototoxic drug eruptions, DM, atopic eczema, seborrheic dermatitis, contact eczema, and rosacea. SCLE lesions need to be

distinguished from photoallergic and phototoxic drug eruptions, as well as from other forms of annular erythemas (erythema annulare centrifugum, erythema gyratum repens, granuloma annulare, eczema, psoriasis, and tinea). Leukoderma in patients with SLE must not be mistaken for vitiligo, whereas hyperpigmented skin lesions in patients with chronic DLE (CDLE) have to be distinguished from other forms of hyperpigmentary skin diseases.

In addition to the previously described LE-specific skin lesions, a plethora of nonspecific skin signs and associated skin diseases can be present in patients with SLE. These skin signs include harmless vascular changes such as nail-fold abnormalities (large and tortuous capillaries together with areas of avascularity), as well as more serious complications such as vasculitis (leukocytoclastic vasculitis, urticarial vasculitis, nodular vasculitis) and other forms of vasculopathy (atrophie blanche, livedo reticularis, Degos-like lesions, ulcerations, and thromboses), the latter developing especially in patients with antiphospholipid syndrome. Nonscarring alopecia (“lupus hair”) may be seen in patients with SLE, whereas scarring alopecia typically occurs in patients with DLE involving the scalp. Raynaud phenomenon, calcinosis cutis, scleroderma-like changes, and rheumatoid nodules may indicate the presence of an overlap syndrome.

Dermatomyositis

Key dermatologic signs of DM include heliotrope rash, Gottron papules, Gottron sign, poikiloderma atrophicum vasculare, periungual telangiectases, dystrophic cuticles, and calcinosis cutis.

Involvement of the skin is essential in making the diagnosis of DM because characteristic cutaneous lesions belong to the diagnostic criteria for DM according to Bohan and Peter.¹¹ Importantly, skin manifestations precede the clinical symptoms of muscle weakness, electromyopathic abnormalities, or increased levels of creatine phosphokinase in 30% of patients with DM, and in 10% to 20% of all patients with DM, specific skin changes may occur for longer than 6 months without systemic involvement. This group of patients has been referred to as having *amyopathic DM* (DM sine myositis). Although a variety of skin manifestations occur in DM, none of the skin signs allows discrimination between idiopathic DM and the paraneoplastic form.

One highly specific skin sign that can be regarded as the cutaneous hallmark feature of DM is the heliotrope rash (Fig. 33.6). This often pruritic, sometimes burning, violaceous, confluent erythema resembles the color of the heliotrope, a pinkish purple flower that tracks the course of the sun. The heliotrope rash of DM has a characteristic distribution that especially involves the periorbital area. Other sites of predilection are the malar area of the face, the posterior aspect of the neck and shoulders (referred to as the “shawl sign”), and the scalp. DM also often affects the extensor surfaces of the extremities, the knuckles, the dorsal aspects of the interphalangeal joints, and the periungual area of the fingers in a symmetric fashion (see



Fig. 33.6 Heliotrope rash on the face in a man with dermatomyositis.

Fig. 148.1). The characteristic violaceous color and the periorbital distribution of the heliotrope rash distinguish DM from the butterfly rash (malar rash) of ACLE. It is also important to recognize that the skin lesions of DM, when affecting the fingers, tend to be located over the joints and not on the interphalangeal areas, as in patients with generalized ACLE (compare Figs. 33.1 and 148.1).

Depending on the intensity of inflammation, the violaceous macules of DM may evolve into plaques that are often covered with a fine silvery scale, especially on the knees and elbows. When such lesions occur over the knuckles, in the interphalangeal joints, and in the periungual area, they are known as *Gottron papules* (see Fig. 148.1). Violaceous macules developing over the knuckles and the elbows or knees have been referred to as the *Gottron sign* (Fig. 33.7). The intensely inflamed skin lesions of DM may develop into erosions, subepidermal blisters, and ulcers (Fig. 33.8). Recently, the presence of antimelanoma differentiation-associated gene 5 (*MDA5*) has been reported to identify the presence of characteristic skin lesions and musculoskeletal, pulmonary, and prognostic features in Japanese patients with DM.¹² Patients with these antibodies had multiple pustules and ulcers on their fingers and palms. Mortality was independently associated with the presence of anti-MDA5 antibodies.

Furthermore, the term *poikiloderma atrophicum vasculare* has been coined to describe patients with DM and a combination of violaceous erythema, hyperpigmentation, hypopigmentation, telangiectasia, and atrophy.

In addition to the aforementioned skin signs, many patients with DM have prominent nail-fold telangiectases (see Fig. 148.8) and dystrophic (“ragged”) cuticles. Moreover, gingival telangiectases have recently been identified as a sign of juvenile DM. Other, less frequently encountered cutaneous manifestations of DM include panniculitis leading to lipotrophy, papular and pustular lesions, and centripetal flagellate erythema. The term *mechanic’s hands* (see Fig. 148.9) has been applied to the occurrence of



Fig. 33.7 Violaceous plaques on the knees of a patient with dermatomyositis (Gottron sign).



Fig. 33.8 Skin ulcerations in a young female with paraneoplastic dermatomyositis.

chronic eczematous skin lesions on the fingers of patients with myositis.¹³ A high proportion of patients with mechanic's hands turned out to have so-called *antisynthetase syndrome* (an overlap syndrome consisting of anti-synthetase antibodies, erosive polyarthritis, interstitial lung disease, fever, Raynaud phenomenon, and inflammatory myositis). Another subset has anti-PM-SCL antibodies, indicative of a polymyositis-scleroderma overlap syndrome. However, recent observations have questioned the specific association of the previously mentioned antibodies with mechanic's hands, thus suggesting that these skin manifestations may also occur in related systemic connective tissue disorders.

Calcinosis cutis can be an extremely painful and devastating skin manifestation of DM. It occurs most often at sites of friction and trauma, such as on the elbows, trochanters, knees, and fingers, and consists of hard, irregular nodules that eventually drain chalky material to the skin surface. It is more prevalent in juvenile DM than in the adult form. Of note, calcinosis is also a key feature of the calcinosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, telangiectasia (CREST) syndrome and can be a manifestation of overlap syndromes.

Histopathologic examination of a heliotrope erythema typically reveals an interface dermatitis with a sparse lymphocytic infiltrate, epidermal atrophy, vacuolar alteration of the basal keratinocytes, basement membrane degeneration, and interstitial mucin deposition. More inflamed lesions (i.e., Gottron papules) also show lichenoid infiltrate and acanthosis of the epidermis. Immunohistologic studies have demonstrated that the infiltrate in skin and muscle lesions of patients with DM consists mainly of CD8+ lymphocytes, thus supporting the concept of a lymphocyte-mediated disease in the pathogenesis of DM.

The differential diagnosis of DM includes SLE, psoriasis, atopic dermatitis, photoallergic and phototoxic drug eruption, contact dermatitis, cutaneous T-cell lymphoma, SSc, and trichinosis. The skin ulcers in DM need to be distinguished from hemorrhagic-necrotizing vasculitis and from a DM-like eruption with painful ulcerations induced by hydroxyurea.

Systemic sclerosis

Key dermatologic signs of SSc include Raynaud phenomenon, symmetric cutaneous sclerosis, finger swelling, sclerodactyly, digital pits and ulcers, dilated or atrophic nail-fold capillaries, calcinosis cutis, and hyperpigmentation.

The term *sclerosis* describes hardening or induration as a result of excessive deposition of interstitial collagen and subsequent tissue fibrosis. By definition, SSc is a multisystem disorder that involves the skin and internal organs. However, it should be noted that sclerosis of the skin ("scleroderma") is a common reaction pattern of several fibrotic skin disorders, some of which are benign and localized only to the skin whereas others are systemic conditions. Thus, in the context of the clinical pattern, internal organ abnormalities, and laboratory tests, the diagnosis of SSc should always exclude these differential diagnoses (see later).

There is striking heterogeneity within the clinical spectrum of cutaneous thickening in patients with SSc, but two subtypes with distinct clinical, serologic, and prognostic features have been delineated. In patients with *diffuse* SSc, skin thickening involves the trunk and proximal portions of the extremities, whereas in patients with *limited* SSc, the skin induration is confined to the face and distal portions of the extremities. However, there are cases with overlap between these two widely accepted clinical forms of SSc. A distinct form of limited SSc with induration of the fingers ("sclerodactyly") is the CREST syndrome. These patients typically have detectable anticentromere antibodies and a generally favorable prognosis when compared with patients with diffuse SSc. Finally, an unusual variant called *scleroderma sine scleroderma*, in which affected patients have evidence of SSc secondary to SSc-related antibodies and internal organ involvement but no skin involvement, has been described. The prognosis of these patients is similar to those with limited SSc.

Often years before the onset of skin induration, patients with SSc experience Raynaud phenomenon (see Figs. 142.2 and 142.3). Although a non-specific sign that is seen in other connective tissue diseases and closely related overlapping syndromes, Raynaud phenomenon is present in 90% to 99% of patients with diffuse or limited SSc. When cutaneous involvement proceeds, an edematous phase of the affected sites often takes place, especially on the fingers ("puffy fingers"). Similar changes may also be seen on the forearms, legs, feet, face, and trunk. This is followed by gradual thickening of the skin in which the initial inflammation is replaced by interstitial fibrosis caused by abnormal collagen metabolism (indurative phase) and subsequent sclerodactyly and dermatopathic contractures. The impaired acral blood flow in sclerodactyly may lead to digital pits and ulcers (see Fig. 142.4). A recent study further revealed that patients with SSc and digital

ulcers exhibited internal organ involvement 2 to 3 years earlier than did those without digital ulcers.¹⁴

Among the other common cutaneous key signs of SSc are telangiectases, which also form a diagnostic cornerstone in patients with CREST syndrome. The telangiectases seen in patients with SSc are often located on the face, including the lips, but may also be detected on the neck, volar aspects of the fingers, and palms and tend to be matted (see Fig. 142.11). Dilated nail-fold capillaries, often alternating with areas of capillary loss, can easily be detected with a dermatoscope. Calcinosis is another key feature of CREST syndrome and tends to be located on the extremities, especially at the fingertips and over joints (Fig. 33.9).

A relatively unappreciated skin sign in patients with SSc is skin hyperpigmentation. It occurs mostly as a diffuse brownish discoloration resembling a suntan and is usually accentuated in areas of friction and pressure (Fig. 33.10). Variants of skin discoloration in patients with diffuse SSc do occur and include "salt and pepper," which describes a combination of hyperpigmentation and hypopigmentation often found on the upper part of the trunk (see Fig. 33.10).

Although a number of instrumental devices such as a skin durometer and 25-MHz ultrasonography may be useful to determine the extent of skin sclerosis in patients with SSc, the modified Rodnan total skin thickness score remains an essential tool for daily routine, as well as for clinical trials. This score assesses cutaneous thickening on a scale of 0 to 3 in 17 anatomic areas by means of palpation.¹⁵ However, interobserver variability is high (mean, 17.7), and proper application of this tool in patients with SSc still requires some training.

Histopathologic examination of sclerotic skin from patients with SSc demonstrates excessive collagen deposits within the dermis and subcutaneous tissue that often entrap the adnexal structures as the predominant



Fig. 33.9 Calcinosis cutis.



Fig. 33.10 Diffuse hyperpigmentation of the skin in a patient with systemic sclerosis. Note also the depigmentation in the submammary region.

finding. In earlier inflammatory phases (edematous phase), a dense lymphocytic infiltrate may be seen at the interface of the deep dermis and adipose tissue.

The differential diagnosis of SSc includes scleromyxedema; eosinophilic fasciitis (Shulman syndrome); scleredema adutorum and diabeticorum; diabetic thick skin; sclerosing chronic graft-versus-host disease; sclerosing forms of porphyria; polyneuropathy, organomegaly, endocrinopathy, *M* component, and skin changes (POEMS syndrome); nephrogenic fibrosing dermopathy; eosinophilia myalgia syndrome; toxic oil syndrome; carcinoid syndrome; pansclerotic localized scleroderma (morphea); exposure to bleomycin, aromatic chlorinated hydrocarbons, or vinyl chloride; phenylketonuria; various progeria syndromes; and reflex sympathetic dystrophy.

Sjögren syndrome (Mikulicz disease, sicca syndrome)

Key dermatologic signs of SjS include xerostomia, xerosis cutis, angular stomatitis (perlèche), various forms of cutaneous vasculitis, and annular erythema.

Mucocutaneous symptoms are usually the first clinical findings in patients with SjS, a systemic autoimmune disorder that primarily affects the secretory glands. Though a nonspecific sign, dryness (xerosis) of the mucous membranes in context with the other diagnostic criteria is a key component for establishing the diagnosis of this multisystem disease. Xerosis can involve not only the mouth (xerostomia) and the eyes (leading to keratoconjunctivitis sicca) but also the vagina. Regarding the mouth, patients typically complain of dryness, soreness, and burning sensations. Vaginal xerosis can likewise result in dryness, burning, and dyspareunia, but patients frequently do not report these symptoms unless asked specifically about them. Because of diminished salivary production, angular stomatitis (perlèche) of the mouth with *Candida* infection is common. Although dental and gingival problems are said to be more frequent in patients with SjS, a recent study did not indicate any increased risk for caries and gingivitis, probably because of increased awareness and dental care of affected patients.¹⁶

In addition to the aforementioned key signs in the mucous membranes, several *bona-fide* skin manifestations are frequently observed in patients with SjS. All of them are again nonspecific. Xerosis cutis is found in 50% of patients, but the underlying pathomechanism remains obscure. It may lead to generalized pruritus. In the authors' experience, various forms of noncutaneous vasculitis, most likely resulting from an immune complex mechanism, are frequently encountered in patients with SjS. They include palpable and nonpalpable purpura on the legs and buttocks (see Fig. 138.5). This form of cutaneous vasculitis is characteristically induced or aggravated by physical exertion. Other forms of cutaneous vasculitis include lymphocytic vasculitis and urticarial vasculitis (either hypocomplementemic or, less commonly, normocomplementemic). By definition, the urticarial lesions of urticarial vasculitis last longer than 48 hours (in contrast to common urticaria) and often have a purpuric component. Patients frequently complain of burning and painful sensations. The lesions often heal with hyperpigmentation. Histologically, the lesions of lymphocytic vasculitis display a mononuclear cell infiltration with disruption of the architecture of the small blood vessels, whereas those of leukocytoclastic vasculitis, including urticarial lesions, show the expected well-described changes.

An unusual skin manifestation of SjS was originally described in Japanese children and has been coined annular erythema of SjS. It appears to be highly associated with the presence of anti-Ro antibodies. Clinically and histologically, these lesions may be indistinguishable from annular SCL. Recent observations indicate that identical lesions can also occur in white individuals.

Regarding other cutaneous manifestations, it is important to note that SjS can be not only primary but also secondary and therefore associated with a number of other diseases, including LE, DM, SSc, RA, primary biliary cirrhosis, fibromyalgia, and others. The specific skin signs of these associated disorders must therefore be distinguished from the *bona-fide* skin manifestations of SjS.

OTHER SYSTEMIC RHEUMATIC DISEASES

Rheumatoid arthritis

Key dermatologic signs of RA include nodules, often symmetrically distributed, purpura, petechiae, and ulcerations.

The characteristic clinical features of RA are frequently associated with skin manifestations, which may not only serve as helpful diagnostic clues

but also indicate the severity of the disease. Rheumatoid nodules, accelerated rheumatoid nodulosis, rheumatoid neutrophilic dermatosis, and rheumatoid vasculitis are regarded as RA-specific skin manifestations.

Classic *rheumatoid nodules* are present in about 25% of patients with RA and are more frequent in the white male population.¹⁷ Most patients with rheumatoid nodules are rheumatoid factor positive. In seronegative RA, the nodular lesions turned out to be mostly granuloma annulare or other palisading granulomas. Genetic predisposition seems to play a role because patients with the HLA-DR4 haplotype and those with heterozygosity for HLA-DRB1 alleles are at high risk for nodular disease, as well as a severe RA prognosis.¹⁸ Rheumatoid nodules measuring from a few millimeters up to several centimeters generally develop as subcutaneous, firm, and painless lesions. Usually they occur on periarticular locations over extensor surfaces, but they may appear in any location, including the lung, heart, and muscle. Complications that may sometimes occur include infection, ulceration, gangrene, bursitis, and synovial rupture.

The differential diagnosis of rheumatoid nodules includes chronic gouty tophi, rheumatic fever nodules, the subcutaneous nodules found in SLE, nodular or keloidal scleroderma, and the nodules seen in necrobiosis lipoidica and granuloma annulare. In addition, tumoral calcinosis, fibromas, xanthomas, subcutaneous sarcoidosis, metastatic tumors, amyloidosis, ganglion cysts, foreign-body granulomas, basal cell carcinomas, epidermoid cysts, and synovial cysts should be considered.

The characteristic symptomatic complex of arthritis, leukopenia, and splenomegaly, which develops in 1% of patients with RA, is known as *Felty syndrome*. Rheumatoid nodules (76%), hyperpigmentation, and therapy-resistant leg ulcers (22%) may also occur.¹⁹ However, cutaneous hyperpigmentation and leg ulceration may be multifactorial and are often related to underlying chronic venous insufficiency. Importantly, Felty syndrome is associated with an increased risk for cutaneous and systemic infections that may be difficult to treat and be the cause of sepsis. The differential diagnosis includes SLE, drug-induced leukopenia, viral infection, amyloidosis, leukemia, lymphoma, subacute bacterial endocarditis, aplastic anemia, splenic abscess, hemolytic anemia, tuberculosis, and SjS. In addition, cutaneous ulcerations and hyperpigmentation may also be caused by systemic treatment with methotrexate (MTX).

Accelerated rheumatoid nodulosis was initially reported in patients receiving MTX therapy for RA or juvenile rheumatoid arthritis.²⁰ It is characterized by the development of painful nodules mainly on the hands of RA patients being treated with MTX; it has not been found to be associated with other immunosuppressive drugs such as azathioprine. RA patients treated with hydroxychloroquine, D-penicillamine, colchicine, or sulfasalazine were found to be protected against the development of MTX-induced accelerated rheumatoid nodulosis. Interestingly, the occurrence of similar nodules has been observed during MTX therapy in a patient with PsA. Recently, accelerated rheumatoid nodulosis has also been described in patients receiving etanercept,²¹ as well as in one patient receiving an aromatase inhibitor,²² thus indicating that MTX is not the only trigger eliciting such skin manifestations of RA. Like other granulomatous skin manifestations of RA (see later), infections by typical and atypical mycobacteria, as well as by opportunistic or endemic bacteria, have to be excluded, especially in patients taking immunosuppressants.

Rheumatoid vasculitis is a late complication of RA that may involve the skin, as well as other organs, and may affect vessels of any size. Accordingly, rheumatoid vasculitis can result in a variety of cutaneous skin signs (Box 33.3). It occurs in seropositive and mainly male RA patients with longstanding disease.²³ Small-vessel disease clinically represents palpable and nonpalpable purpura, localized petechiae, splinter hemorrhages, nail-fold infarctions (Bywaters lesions), and peripheral neuropathy. In medium-vessel disease, cutaneous findings include nodules, ulcerations, livedo reticularis, and digital infarcts. Because the course of rheumatoid vasculitis is associated with high morbidity and mortality, early and intensive immunosuppressive therapy is required. Biopsy of cutaneous lesions, preferentially nodules, and immunohistochemical examination are often helpful in establishing the diagnosis. Because peripheral neuropathy is frequently observed in cases in which vasculitis cannot be identified, nerve conduction studies and sural nerve or muscle biopsy can be performed. The differential diagnosis of rheumatoid vasculitis includes polyarteritis nodosa, PG, SLE, antineutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis, and erythema elevatum et diutinum.

In addition to the previously mentioned specific skin manifestations of RA, large numbers of nonspecific skin signs and associated dermatoses have been described (Box 33.4). *Pyoderma gangrenosum* is frequently associated with both seronegative and seropositive RA. Clinically, it begins as a tender erythematous or violaceous papule that expands rapidly into a purulent necrotic ulcer with ragged edematous edges (Fig. 33.11). Usually, PG occurs

BOX 33.3 SKIN MANIFESTATIONS OF RHEUMATOID VASCULITIS

Petechiae or purpura
 Digital infarcts
 Nail-fold telangiectases and infarctions
 Gangrene
 Nonspecific maculopapular or nodular erythema
 Hemorrhagic blisters
 Livedo reticularis
 Erythema elevatum et diutinum
 Atrophie blanche
 Allergic venulitis
 Necrotizing granulomatous vasculitis
 Urticaria vasculitis

BOX 33.4 NONSPECIFIC SKIN MANIFESTATIONS AND ASSOCIATED SKIN DISORDERS IN RHEUMATOID ARTHRITIS

Pyoderma gangrenosum
 Palisaded neutrophilic and granulomatous dermatitis
 Interstitial granulomatous dermatitis
 Atrophic and fragile skin
 Pale and transparent skin
 Palmar erythema
 Livedoid (Raynaud-like) fingertips
 Onychorrhexis and clubbing of the nails
 Onycholysis
 Periungual erythema
 Yellow nail syndrome
 Splinter hemorrhages and nail-fold thromboses
 Pressure ulcers
 Hyperpigmentation
 Transient macular erythema
 Erythromelalgia
 Noninflammatory purpura
 Erythema multiforme
 Urticaria
 Erythema nodosum
 Vitiligo
 Alopecia areata
 Nonmelanoma skin cancer
 Intralymphatic histiocytosis of the skin

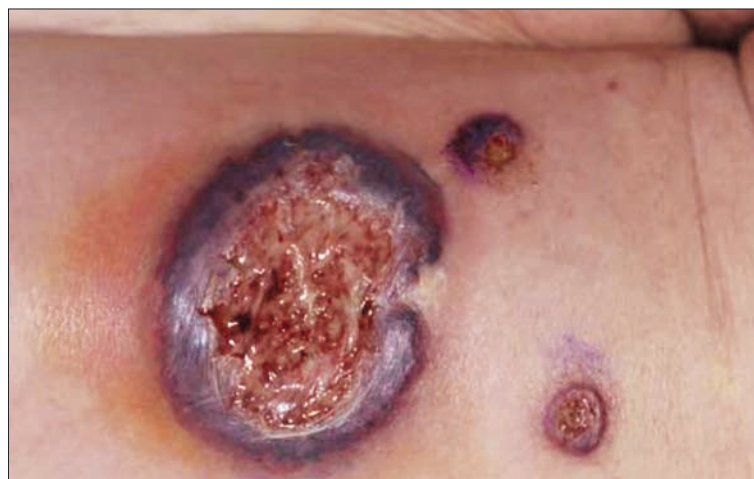


Fig. 33.11 Pyoderma gangrenosum. Note the undermined hemorrhagic borders.

as a single painful lesion on the lower extremities. Koebner and pathergy phenomena are characteristic. The presence of chronic relapsing lesions in unusual sites such as the face, upper extremities, or abdomen may indicate another underlying disease such as inflammatory bowel disease or hematologic disorders. The idea that PG is a true skin manifestation of RA has been challenged because it also occurs in other systemic disorders, has no relationship in its clinical manifestation with the course of RA, and involves no



Fig. 33.12 Rope sign in a patient with interstitial granulomatous dermatitis.

histology specific for RA.²⁴ Histologic examination of early lesions demonstrates a neutrophilic infiltrate and small abscesses.

The differential diagnosis of PG includes venous or arterial ulcers, vasculitis, drug reactions, antiphospholipid syndrome, halogenoderma, factitial diseases, deep fungal infections, mycobacterial infections, gummatous syphilis, viral infections, amebiasis, arthropod bites, and tumors.

Rheumatoid neutrophilic dermatosis is a rare cutaneous sign in patients with severe and seropositive RA.²⁵ Clinically, it is manifested as asymptomatic erythematous urticarial papules and plaques that may persist and sometimes ulcerate. They are usually distributed on the forearms and hands. Rheumatoid neutrophilic dermatosis resembles Sweet syndrome.

Palisaded neutrophilic and granulomatous dermatitis, also known as Winkelmann granuloma, represents a condition of unknown cause with a variety of clinical findings in the context of systemic diseases. Skin manifestations usually develop symmetrically on the extensor surfaces of the elbows and fingers and appear as skin-colored, erythematous, or violaceous papules, nodules, and plaques, sometimes with central umbilication and crusts or perforation.²⁶ Histopathologic examination shows granulomatous inflammation in the presence or absence of leukocytoclastic vasculitis. In addition to RA, this condition has been especially associated with Behçet disease, SLE, SSC, ulcerative bowel and celiac disease, sarcoidosis, ANCA-associated vasculitis (“Wegener granulomatosis”), and lymphoproliferative disease.

Another skin sign of RA may be *interstitial granulomatous dermatitis*.²⁷ It consists of multiple well-demarcated erythematous to violaceous papules or plaques, sometimes coalescing to larger areas or linear cords (Fig. 33.12). However, the latter distinctive pattern (“rope sign”) is seen in only 10% of all cases.²⁸ Lesions are typically located on the trunk but may also occur on the proximal ends of limbs. They may perforate with extrusion of the necrobiotic collagen. Histopathologically, the lesions consist of a predominantly CD68+ inflammatory infiltrate of macrophages between collagen bundles in the mid and deep dermis. The macrophages are surrounded by degenerated collagen fibers, and no signs of vasculitis or mucin deposition are present. Giant multinucleated histiocytes are detectable in only a subset of cases.²⁸ It is important to note that this condition is associated not only with RA or other forms of arthritis or arthralgias but also with other autoimmune diseases and with cancer.²⁸ The differential diagnosis of the granulomatous dermatitis of RA includes mainly granuloma annulare, necrobiosis lipoidica, granulomatous slack skin, and interstitial granulomatous drug reactions.

Systemic-onset juvenile rheumatoid arthritis (juvenile rheumatoid arthritis, juvenile chronic arthritis, Still disease)

Key dermatologic signs of SOJRA include macular or maculopapular exanthema and rheumatoid nodule-like lesions.



Fig. 33.13 Exanthema in a child with Still disease.

Diagnosis of SOJRA can be challenging. Because skin manifestations can precede the arthralgias by years, early recognition can be crucial in establishing the diagnosis. SOJRA has two clinical manifestations: an acute febrile systemic variant and an oligoarticular variant with low-grade persistent fevers. In the acute-onset variant, in which high episodic fevers with temperatures higher than 38.9° C are characteristic, a nonpruritic transient exanthema that recurs with fevers develops in 90% of patients.²⁹ It consists of discrete macular or maculopapular lesions, often located on the trunk (Fig. 33.13). The color of the lesions is pink to red, and koebnerization is common. The histopathologic findings of the rash are nonspecific and consist of a discrete perivascular mixed infiltrate with edema of the upper dermis. Another skin sign in patients with SOJRA is rheumatoid nodule–like lesions with a predilection for the extensor surfaces of the extremities.³⁰ Lesions can be both clinically and histologically indistinguishable from those in patients with RA.

The differential diagnosis of the typical exanthema of SOJRA in combination with fever and arthralgias includes rheumatic fever, familial Mediterranean fever, hyper-IgD syndrome, tumor necrosis factor receptor–associated periodic syndrome (TRAPS), familial Hibernian fever, autosomal dominant periodic fever with amyloidosis, and benign autosomal dominant familial periodic fever.

Relapsing polychondritis (atrophic polychondritis, systemic chondromalacia, polychondropathia)

Key dermatologic signs of RP include erythema, swelling, and pain in the cartilaginous portion of the ear with sparing of the earlobe, as well as auricular and nasal deformity.

RP is a chronic inflammatory multisystem disorder that can lead to significant morbidity because of destruction of the cartilaginous tissue in many organs. In a significant number of patients with RP, cutaneous involvement is the first clinical manifestation.

The hallmark cutaneous features of RP are erythema, swelling, and pain in the cartilaginous part of the ear that typically spares the earlobe (see Fig. 167.1). The vast majority of patients with RP suffer from auricular involvement during the course of their disease. Persistent inflammation will lead to destruction of the auricular cartilage and result in so-called cauliflower ears. Involvement of the nasal cartilage occurs in 70% of affected patients and eventually leads to a saddle nose deformity.³¹ Glomerulonephritis may accompany RP.

Histopathologic examination of inflamed cartilage shows basophilic staining, loss of the normal lacunar structures, and a neutrophilic infiltrate. At later stages, lymphocytes and plasma cells are more prominent and the cartilage is replaced by granulation tissue and fibrosis.

Several nonspecific skin signs have been reported to occur in 36% of patients with RP.³² However, a significant proportion may be related to associated diseases (myelodysplastic syndrome, Behçet disease, and other systemic disorders) or adverse effects of concomitant systemic treatment. These skin manifestations consist of various forms of vasculitis, including palpable purpura, and erythema elevatum et diutinum, noninflammatory vasculopathies like livedo reticularis, furthermore, panniculitis, and aphthosis (oral or complex).

The differential diagnosis of RP includes primarily traumatic and infectious forms of chondritis and ANCA-associated granulomatous vasculitis,



Fig. 33.14 Psoriasis vulgaris. Note the typical distribution over the extensor surfaces and silvery scales.



Fig. 33.15 Psoriasis vulgaris involving the scalp (psoriasis capitis).

which may also lead to cartilage destruction, especially of the nose. The combination of features of RP and Behçet disease has led to the designation mouth and genital ulceration with inflamed cartilage (MAGIC syndrome).³³

Psoriatic arthritis

Key dermatologic signs of psoriasis are papulosquamous plaques on the scalp and on the extensor surfaces of the body as well as nail dystrophy. Psoriasis, one of the most common immune-mediated inflammatory skin disorders with an estimated prevalence of 2% in Europe,³⁴ has to be excluded in all patients with arthralgia. Although clinical diagnosis of psoriasis is easy in most cases, it can be challenging in patients with less frequent psoriasis subtypes as well as in those receiving immunosuppressive agents. Moreover, the dermatologic manifestations of psoriasis are quite heterogeneous. Classification of the clinical subtypes of psoriasis is traditionally based on morphology, localization, and extent of the disease, with current concepts also trying to incorporate disease stability and numeric parameters.³⁵

The most common form of psoriasis is known as *psoriasis vulgaris* or *plaque psoriasis*. Its key feature is a sharply demarcated red to pinkish papulosquamous plaque of any size with a noncoherent silvery scale (Fig. 33.14). Involvement of the scalp by psoriasis appears to particularly be associated with PsA (Fig. 33.15).³⁶ On removal of the scale a glossy erythema with blood droplets appears (Auspitz sign). Typically, the elbows, knees, lower part of the back, scalp including the ears, and umbilicus are involved. The palms and soles may be affected as well. Within the psoriasis vulgaris group two subtypes had already been distinguished more than 20 years ago. In the first group (type I), the peak onset of psoriasis occurs at an age of 16 years (females) or 22 years (males), and in the second group (type II) the peak onset occurs at an age of 60 years (females) or 57 years (males).³⁷ Patients



Fig. 33.16 Nail psoriasis. Note the onycholysis, oil spots, and pits.



Fig. 33.17 Psoriasis inversa. Note well-demarcated erythema and absence of scales.

classified as having type I psoriasis vulgaris have a genetic association within the major histocompatibility complex class I region on chromosome 6p (HLA-Cw*0602), whereas patients classified as having type II have no evidence of association with HLA-C alleles.³⁸

Guttate psoriasis (from Latin *guttata*, meaning “droplike”) may be considered a subtype of type I psoriasis vulgaris and is often encountered in children and young adults. In this case the psoriasis develops as an acute eruption of papules and plaques measuring less than 1 cm that most often starts on the trunk but may spread to the proximal parts of the extremities and face. Infections with group B hemolytic streptococci (tonsillitis, pharyngitis) may precede the development of guttate psoriasis, especially in children and young adults. Even though this form of psoriasis is said to be self-limited and resolves within 3 to 4 months, few data are available on the long-term risk for the development of chronic plaque psoriasis after a single episode of guttate psoriasis.³⁹

Nail psoriasis can be considered an important indicator of PsA. Although it occurs in 40% to 45% of patients with psoriasis without joint involvement, its prevalence is 60% to 90% in those with PsA.⁴⁰⁻⁴² Typical features are oil spots (yellow to orange subungual discolorations), pits (punctate nail plate defects), onycholysis, and onychodystrophy (Fig. 33.16). Interestingly, nail psoriasis may be present without additional signs of skin involvement.

In addition to manifestation of psoriasis on the scalp and nails, involvement of the flexural or intertriginous areas may alert the clinician to PsA.³⁶ This type of psoriasis has been coined *psoriasis inversa* and describes the localization of psoriatic lesions in the groin, axilla, submammary region, natal cleft, and genital area. The lesions are typically erythematous with little or no scaling and tend to be associated with maceration and fissuring (Fig. 33.17).

Psoriatic erythroderma describes total involvement of the skin with psoriasis. It is characterized by generalized erythema and various degrees of scaling, depending on the course of development either as an abruptly evolving psoriasis or as a complication of preexisting, slowly progressive plaque psoriasis. Psoriatic erythroderma must be considered a potentially life-threatening condition associated with hypothermia, hypoalbuminemia, and tachycardia. It may lead to high-output cardiac failure, especially in multimorbid patients.

Pustular psoriasis occurs as a limited eruption of sterile pustules on the palms and soles (psoriasis pustulosa palmoplantaris) or as a generalized form (von Zumbusch psoriasis). The latter is an acute, often febrile eruption of multiple monomorphic sterile pustules on erythematous skin, especially over the trunk and extremities, and is associated with systemic illness. Although psoriasis pustulosa palmoplantaris is frequently found in patients with psoriasis vulgaris, genetic studies point toward a different pathogenesis.⁴³

Assessment of the extent, severity, and acuity of skin involvement by psoriasis can be done with various outcome tools, including the Psoriasis Area and Severity Index, Overall Lesion Severity instrument, physician global assessment, and assessment by affected body surface area. Because psoriasis can severely affect quality of life, patient-related outcome tools are likewise important. For nail involvement, a Nail Psoriasis Severity Index has also been developed.⁴⁴

The diagnosis of psoriasis is made primarily clinically, and skin biopsy is not usually required. If biopsied, early psoriasis lesions show a modest lymphocytic perivascular infiltrate with prominent vessels in the upper dermis. Later, extravasation of erythrocytes occurs with mild epidermal hyperplasia. Scaly lesions reveal epidermal parakeratosis and hyperplasia, prominent mitoses in basal keratinocytes, and neutrophilic infiltration. The neutrophils migrate into the epidermis (Munro microabscesses). Fully developed psoriasis lesions show elongation of the rete ridges, mounds of parakeratosis, and more prominent accumulation of neutrophils. Vessels in the papillary dermis are tortuous and dilated with extravasation of both erythrocytes and lymphocytes.

The differential diagnosis of psoriasis vulgaris includes tinea corporis, papulosquamous SCLE, mycosis fungoides, pityriasis versicolor, pityriasis rubra pilaris, secondary syphilis, and eczema. Psoriasis of the scalp must be distinguished from DLE and tinea capitis, whereas nail psoriasis must be differentiated from tinea unguium. Psoriasis inversa may be mimicked by intertrigo, candidiasis, and Hailey-Hailey disease. Psoriatic erythroderma must be differentiated from other forms of primary (drug-induced) and secondary erythroderma (caused by nonpsoriatic immune-mediated inflammatory skin diseases). Pustular psoriasis needs to be distinguished from bacterial skin infections and other noninfectious pustuloses of the skin.

REFERENCES

- Cardinali C, Caproni M, Bernacchi E, et al. The spectrum of cutaneous manifestation in lupus erythematosus—the Italian experience. *Lupus* 2000;9:417-23.
- Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. *J Am Acad Dermatol* 1981;4:471-5.
- Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. *Best Pract Res Clin Rheumatol* 2004;18:429-62.
- Lowe G, Henderson CL, Grau RH, et al. A systematic review of drug-induced subacute cutaneous lupus erythematoses. *Br J Dermatol* 2011;164:465-72.
- Petri M. Lupus in Baltimore: evidence-based “clinical pearls” from the Hopkins Lupus Cohort. *Lupus* 2005;14:970-3.
- Kuhn A, Bein D, Bonsmann G. The 100th anniversary of lupus tumidus. *Autoimmun Rev* 2009;8:441-8.
- Kuhn A, Richter-Hintz D, Oslislo C, et al. Lupus erythematosus tumidus—a neglected subset of cutaneous lupus erythematosus: report of 40 cases. *Arch Dermatol* 2000;136:1033-41.
- Martens PB, Moder KG, Ahmed I. Lupus panniculitis: clinical perspectives from a case series. *J Rheumatol* 1999;26:68-72.
- Viguier M, Pinquier L, Cavalier-Bailloy B, et al. Clinical and histopathologic features and immunologic variables in patients with severe chilblains. A study of the relationship to lupus erythematosus. *Medicine (Baltimore)* 2001;80:180-8.
- Kuhn A, Amler S, Beissert S, et al. Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index (RCLASI): a modified outcome instrument for cutaneous lupus erythematosus. *Br J Dermatol* 2010;163:83-92.
- Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344-7.
- Koga T, Fujikawa K, Horai Y, et al. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody for predicting the prognosis of Japanese patients with DM. *Rheumatology* 2012;51:1278-84.

13. Stahl NI, Klippel JH, Decker JL. A cutaneous lesion associated with myositis. *Ann Intern Med* 1979;91:577-9.
14. Sunderkötter C, Herrgott I, Brückner C, et al. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. *Br J Dermatol* 2009;160:835-43.
15. Clements P, Lachenberg P, Siebold J, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatology* 1995;22:1281-5.
16. Boutsis EA, Paikos S, Dafni UG, et al. Dental and periodontal status of Sjögren's syndrome. *J Clin Periodontol* 2000;27:231-5.
17. Ziff M. The rheumatoid nodule. *Arthritis Rheum* 1990;33:761-7.
18. Ahmed SS, Arnett FC, Smith CA, et al. The HLA-DRB1*0401 allele and the development of methotrexate-induced accelerated rheumatoid nodulosis: a follow-up study of 79 Caucasian patients with rheumatoid arthritis. *Medicine (Baltimore)* 2001;80:271-8.
19. Sienknecht CW, Urowitz MB, Pruzanski W, et al. H. Fely's syndrome. Clinical and serological analysis of 34 cases. *Ann Rheum Dis* 1977;36:500-7.
20. Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986;29:822-31.
21. Cunnane G, Warnock M, Fye KH, et al. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. *Arthritis Rheum* 2002;47:445-9.
22. Chao J, Parker BA, Zwaifler NJ. Accelerated cutaneous nodulosis associated with aromatase inhibitor therapy in a patient with rheumatoid arthritis. *J Rheumatol* 2009;36:1087-8.
23. Voskuyl AE, Zwinderman AH, Westedt ML, et al. Factors associated with the development of vasculitis in rheumatoid arthritis: results of a case-control study. *Ann Rheum Dis* 1996;55:190-2.
24. Von Den Driesch P. Pyoderma gangrenosum: a report of 44 cases with follow-up. *Br J Dermatol* 1997;137:1000-5.
25. Ichikawa MM, Murata Y, Higaki Y, et al. Rheumatoid neutrophilic dermatitis. *Eur J Dermatol* 1998;8:347-9.
26. Sanguenza OP, Caudell MD, Mengesha YM, et al. Palisaded neutrophilic granulomatous dermatitis in rheumatoid arthritis. *J Am Acad Dermatol* 2002;47:251-7.
27. Long D, Thiboutot DM, Majeski JT, et al. Interstitial granulomatous dermatitis with arthritis. *J Am Acad Dermatol* 1996;34:957-61.
28. Peroni A, Colato CD, Schena D, et al. Interstitial granulomatous dermatitis: a distinct entity with characteristic histological and clinical pattern. *Br J Dermatol* 2012;166:777-83.
29. Calabro JJ, Marchesano JM. Rash associated with juvenile rheumatoid arthritis. *J Pediatr* 1968;72:611-9.
30. Lubbe J, Hofer M, Chavaz P, et al. Adult-onset Still's disease with persistent plaques. *Br J Dermatol* 1999;141:710-3.
31. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and review of the literature. *Medicine (Baltimore)* 1976;55:193-215.
32. Frances C, El Rassi R, Laporte JL, et al. Dermatological manifestations of relapsing polychondritis. A study of 200 cases at a single center. *Medicine (Baltimore)* 2001;80:173-9.
33. Firestein GS, Gruber HE, Weisman MH, et al. Mouth and genital ulcers with inflamed cartilage: MAGIC syndrome. Five patients with features of relapsing polychondritis and Behçet's disease. *Am J Med* 1985;79:65-72.
34. Schäfer T. Epidemiology of psoriasis. Review and the German perspective. *Dermatology* 2006;212:327-37.
35. Griffiths CE, Christophers E, Barker JN, et al. Classification of psoriasis vulgaris according to phenotype. *Br J Dermatol* 2007;156:258-62.
36. Dhir V, Aggrawal A. Psoriatic arthritis: a critical review. *Clin Rev Allergy Immunol* 2013;44:141-8.
37. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol* 1985;13:450-56.
38. Allen MH, Ameen H, Veal C, et al. The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. *J Invest Dermatol* 2005;124:103-6.
39. Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? *Arch Dermatol* 1996;132:717-8.
40. Gladman DD, Anhorn KA, Schachter RK, et al. HLA antigens in psoriatic arthritis. *J Rheumatol* 1986;13:586-92.
41. Gladman DD, Shuckett R, Russell ML, et al. Psoriatic arthritis (PSA)—an analysis of 220 patients. *Q J Med* 1987;62:127-41.
42. Elkayam O, Ophir J, Yaron M, et al. Psoriatic arthritis: interrelationships between skin and joint manifestations related to onset, course and distribution. *Clin Rheumatol* 2000;19:301-5.
43. Asumalahti K, Ameen M, Suomela S, et al. Genetic analysis of PSORS1 distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol* 2003;120:627-32.
44. Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. *Am Acad Dermatol* 2003;49:206-12.