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Preface

This issue of the Giornale Italiano di Dermatologia e Venereologia contains a special section on the dermatological aspects of Connective Tissue Diseases (CTDs). The aim of this section is to focus the readers’ interest on the clinical and pathogenetical aspects of different CTDs such as dermatomyositis, systemic scleroderma, and lupus.

In the context of a multidisciplinary approach, in fact, dermatologists play an important role in the management of these diseases, together with rheumatologists and other specialists.

The papers by Prof. Luger and Prof. Bohm will introduce the cutaneous manifestations of rheumatic diseases from a clinical and pathogenetical point of view.

Healthcare providers who deal with CTDs may also be interested in the clinical description of the common and uncommon cutaneous signs of adult dermatomyositis (discussed by Auriemma et al.) and childhood dermatomyositis (presented by Feliciani et al.).

In a review of the literature, Di Rollo et al. will correlate the principal cutaneous features associated with paraneoplastic dermatomiositis. Abeni et al. present the validation of a QoL assessment tool in its Italian version for systemic sclerosis patients. Parodi et al. will focus on the cutaneous aspects of lupus erythematosus.

Finally, highly experienced dermatologists such as Prof. Vena, Dr. Cassano, Prof. Fargnoli and Prof. Caproni will discuss different aspects of CTDs such as hair involvement, the risk of skin cancer and induction by drugs.

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Cutaneous manifestations of rheumatic diseases. Clinical presentation and underlying pathophysiology

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Being the largest organ of the human body, skin is frequently affected in many rheumatic diseases. Thus, it can serve as an important indicator for the correct diagnosis of a rheumatic disease and also as a marker of disease activity in distinct rheumatic disorders. In this review we will highlight the clinical features of these cutaneous manifestations of the major rheumatic diseases. We will also provide an update on the complex pathobiology of these diseases based on the most recent developments in clinical and translational research.

Key words: Skin - Rheumatic diseases - Lupus erythematosus, systemic - Scleroderma, systemic.

Skin changes occur in a large proportion of patients with rheumatic diseases. They are thus clinically highly important for both dermatologists and rheumatologists. Not only can they guide clinicians to the correct diagnosis of a particular rheumatic disease but may also serve as an indicator for disease activity. Due to the function of skin as a barrier organ to the patient’s outer world it is also essential to be aware of the psychosocial burden chronic and often mutilating skin changes may elicit in patients with rheumatic diseases.

In this review we will highlight cutaneous manifestations of the major systemic rheumatic diseases. The focus of the clinical part of this review will be on so-called specific skin changes, i.e., those lesions that display characteristic and sometimes even pathognomonic features along with a typical histopathology encountered, e.g., Gottron’s papules in dermatomyositis. These specific skin changes have to be differentiated from non-specific skin signs which occur in a diversity of rheumatic as well as in non-rheumatic systemic diseases. In addition to specific and non-specific skin signs a variety of other skin diseases have been noted to be associated in more or less frequency with rheumatic diseases. Due to limitations in space it will be beyond the scope of this review to present all cutaneous manifestations of rheumatic diseases. The major connective tissue disorders are in the centre of this review followed by more often encountered rheumatic diseases with systemic involvement.

Major systemic connective tissue disorders

Systemic lupus erythematosus

Changes of the skin, mucous membranes and hair are common signs in patients with systemic lupus erythematosus (SLE). Approximately 72-85% of patients with SLE suffer from those changes. Moreover, they may represent the first sign of the disease in 23-28% of the patients with SLE. The traditional criteria of the American College of Rheumatology (ACR) for SLE included four dermatologic manifestations: malar rash, photosensitivity, discoid lesions, and oral ulcers. However, patients may fulfil four of these criteria based solely on dermatologic
findings without having other signs for a systemic involvement. In order to improve the specificity and clinical relevance of these cutaneous symptoms, the Systemic Lupus International Collaborating Clinics (SLICC) revised the ACR criteria in 2012 and proposed 17 clinical and immunological criteria. Importantly, non-scarring alopecia was added, whereas "photosensitivity" is no longer included. However, the SLICC criteria still have to be evaluated in routine clinical practice.

Classification of cutaneous lupus erythematodes (CLE) remains complex. Notably, similar types of skin lesions may occur in both SLE and patients with non-systemic forms of LE. The most widely accepted classification of CLE distinguishes 3 major subtypes based on disease activity: acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE). Moreover, extent of skin involvement (local versus generalized) and localization of the inflammatory infiltrate in the skin is indicated (e.g. LE panniculitis indicating LE-specific infiltration of the adipose tissue). Intermediate CLE, formerly known LE tumidus has been suggested as another distinct subtype and a revised classification system has been proposed accordingly (Table I). Importantly, patients with SLE or CLE may carry simultaneously different LE-specific skin lesions, e.g. a butterfly rash plus chilblain LE, the latter a variant of CCLE (v. i.). To better monitor the type and extent of CLE lesions the Cutaneous Lupus Area and Severity Index (CLASI) has been proposed. Albeit time-consuming in routine daily practice it may be especially helpful for systematic epidemiologic and therapeutic studies.

The hallmark lesion of ACLE in patients suffering from SLE is malar dermatitis (malar rash, butterfly rash). It describes a reddish maculopapular eruption in a characteristic butterfly distribution of the face (Figure 1). The eruption often extends symmetrically onto both cheeks and the nose. The forehead may be involved but the nasolabial folds are typically spared. Patients frequently report induction or exacerbation of this type of CLE by ultraviolet (UV) light exposure indicating photosensitivity as an important diagnostic clue as well as a pathogenetic component. Lesions are often transient and last from hours to weeks. Healing is without scarring. ACLE may become generalized involving the trunk with accentuation of the UV-exposed areas (Figure 2) but may be localized elsewhere including the dorsal parts of the hands and fingers. Knuckles are typically spared. A life-threatening variant of generalized ACLE is toxic epidermal necrolysis (TEN)-like ACLE. Here, massive epidermal injury occurs due to severe alterations of the dermoepidermal junction with subsequent keratinocyte damage. Another variant is Rowell’s syndrome. It was originally described as an erythema multiforme-like eruption in patients with DLE and positive anti-Ro/La antibodies. However, similar skin lesions may also develop in patients with SLE, SCLE and in presence or absence of anti-Ro/La anti-

![Figure 1](image-url).—Malar rash with typical butterfly distribution in a young woman with SLE.
located in UV-exposed skin including the lateral aspects of the face: the “V” of the neck as well as of the upper ventral and dorsal part of the trunk, and the dorsolateral aspects of the forearms (Figure 4). SCLE lesions may heal with residual hypo- or depigmentation and the resulting picture may be mistaken for vitiligo. Scarring, on the other hand, is not a feature of SCLE. Many patients with SCLE may have mild systemic symptoms including arthralgias and musculoskeletal complaints. Accordingly, the percentage of patients with SCLE fulfilling four or more ACR criteria for SLE ranges from 30% to 62%. A recent study in a Swedish population revealed that about 38% of SCLE cases may be associated with certain drugs. The most common agents include terbinafine, tumor necrosis factor-α (TNF-α) inhibitors, antiepileptics, proton-pump inhibitors, thrombocyte inhibitors, angiotensin-converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory drugs (Figure 5). Importantly, drug-induced SCLE resolves after discontinuation of the triggering medication.

The key features of skin lesions of CCLE, also known as discoid LE (DLE) are erythema, hyper-
Epidermal hyperkeratosis is the hallmark feature in hypertrophic/verrucous CCLE and results in thick scaly lesions. LE panniculitis describes an intense inflammation of the adipose tissue of the skin leading to indurated plaques and lipatrophy. Often these lesions are encountered in the face, proximal parts of the extremities, upper trunk and buttocks. When the overlying dermis and epidermis is also involved this is referred to as LE profundus. As shown by a retrospective study of 40 patients with this CCLE variant only 10% of patients fulfilled the ACR criteria for SLE. Another variant of CCLE is chilblain LE. Lesions consist of red to violaceous plaques located on the distal parts of the extremities (fingertips, toes but also occasionally on other parts of the body). They are typically induced and aggravated by cold exposure but are also found during the summer time Figure 8. Patients with this CLE subtype should be carefully followed-up as up to 24% of them will develop SLE. Finally, the term LE tumidus has been applied for photosensitive erythematous, sometimes urticarial plaques and nodules without epidermal hyperkeratosis or follicular plugging Figure 9. These lesions are often transient for which the term intermediate CLE has been proposed. Lesions are often found on the face, upper trunk and extremities. Most patients with LE tumidus do not have antinuclear antibodies and diagnosis relies on the clinical and histomorphological picture. Rarely patients with LE tumidus develop SLE. The exact pathogenesis of the various LE-specific skin manifestations is complex and incompletely understood. A complex interplay between a predispos-
miR-146a, a negative regulator of the interferon (IFN) pathway, has found to be significantly under-expressed in patients with SLE and be inversely correlated with disease activity. MiR-146a regulates the type I IFN pathway through interaction with various key molecules, e.g. the interferon regulatory factor 5 (IRF-5), signal transducer and activator of transcription (STAT)-1, interleukin (IL)-1 receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6). Interestingly, a haplotype of IRF-5 is associated with increased susceptibility to LE in multiple ethnic backgrounds. Moreover, an altered DNA-methylation of T-cells, triggered from drugs, UV light or diet, may induce a flair of LE in susceptible individuals. Estrogens as well as the presence of two X chromosomes seem to mediate an increased susceptibility for LE in women. In those, one X chromosome may be inactivated via epigenetic DNA methylation. Demethylation of specific sequences in the X chromosome in women with LE may alter gene expression and contribute to the female predominance of the disease.

Several studies suggest multiple factors including dysregulated innate and adaptive immune mechanisms as well as chemokine and cytokine imbalances in the etiopathogenesis of LE. Activation of toll-like-receptors (TLRs), such as TLR-7, through recognition of endogenous ligands seems to induce proinflammatory signals including type I IFN pathways. Type I as well as type III IFN and myxovirus protein A seem to play a key pathogenic role in UVB-induced and genuine CLE.
lesions. Decreased numbers of regulatory T-cells (Tregs) may further contribute in weakening immune tolerance. An increased susceptibility of keratinocytes to UV-induced cell death in combination with decreased clearing of apoptotic debris due to impaired phagocytic capacity of macrophages may mediate the development of cutaneous LE lesions by sun exposure. Interestingly, data from in vitro studies demonstrate that UVB irradiation of human keratinocytes is capable of translocating autoantigens such as Ro to the plasma membrane possibly making them accessible for circulating autoantibodies and leading to activation of apoptotic pathways. Several other lines of evidence suggest that autoantibodies detected in patients with LE appear to play an important role in the development of LE-specific skin lesions. Accordingly, it is well known that pregnant women with circulating anti-Ro antibodies may deliver babies with SCLE-like lesions (neonatal LE) that are indistinguishable from the skin lesions seen in adults. Another crucial pathogenetic factor that is closely related to the occurrence of skin lesions of LE is complement C1q. Complete deficiency of C1q is a major risk factor for the development SLE and most individuals with homozygous congenital deficiency of C1q develop early-onset SLE with cutaneous LE-like lesions (neonatal LE) that are indistinguishable from the skin lesions seen in adults.

Another crucial pathogenetic factor that is closely related to the occurrence of skin lesions of LE is complement C1q. Complete deficiency of C1q is a major risk factor for the development SLE and most individuals with homozygous congenital deficiency of C1q develop early-onset SLE with cutaneous LE-like lesions. Accordingly, deficiency in C1q may result in altered clearance of autoantigens and immune complexes associated with UVB-exposed or cytokine-stimulated epidermal keratinocytes. Finally, there is also some recent evidence for a role of TNF-α in the pathogenesis of LE. Anti-TNF-α treatment of patients with other immune-mediated inflammatory diseases can result in the occurrence of autoantibodies, lupus-like syndrome and in rare cases even to the development of LE or dermatomyositis.

In addition to UV light, smoking is considered a potential trigger factor for CLE. Smoking alters the metabolism of the aminoquinolene antimalarials (chloroquine and hydroxychloroquine), the most frequently used therapeutics against CLE. Other studies have shown that low but measurable amounts of UVB can be emitted from compact fluorescent lights, suggesting covering of these by patients with lupus.

A skin biopsy specimen may be helpful to establish the diagnosis of CLE and to rule out other differential diagnoses (v.i.). However, the correct classification of the various CLE subtypes relies primarily on the clinical picture and laboratory parameters. Notably, histological changes may be subtle during the initial phase of patients with CLE. Histopathologically, ACLE shows various degrees of cellular damage of scattered epidermal keratinocytes (either hydropic change or eosinophilic appearance) together with edema and a sparse lymphohistiocytic infiltrate of the upper dermis. The dermal blood vessels are often dilated with extravasation of erythrocytes. SCLE displays hypodermic and eosinophilic changes of basal epidermal keratinocytes often with epidermal atrophy. There is a lymphohistiocytic infiltrate in the upper dermis with an interface and perivascular pattern. DCLE lesions have additional epidermal hyperkeratosis and thickening of the dermal-epidermal and follicular basement membranes. The lymphohistiocytic infiltrate is often prominent involving hair follicles. Dermal deposition of mucin is a frequent finding. Deeper forms of CCLE are characterized by lymphohistiocytic infiltrates in the lower dermis (LE tumidus) or within while subcutaneous fat (LE panniculitis).

Depending on the subtype of CLE the differential diagnoses include erythema solare, photoallergic and phototoxic drug eruptions, dermatomyositis, atopic eczema, seborrheic dermatitis, contact eczema and rosacea, annular erythemas (erythema annulare centrifugum, erythema gyratum repens), granuloma annulare, eczema, psoriasis, and tinea.

There are a number of non-specific skin signs and associated skin diseases which may occur in patients with LE, especially SLE. These skin signs encompass harmless vascular changes such as nail fold abnormalities (large and tortuous capillaries together with areas of avascularity) but also more serious complications such as vasculitis (leucocytoclastic vasculitis, urticarial vasculitis, nodular vasculitis) and vasculopathy (atrophic blanche, livedo reticularis, Degos’ disease-like lesions, ulcerations, thrombosis). The latter may develop more often in patients with concomitant antiphospholipid syndrome. Non-scarring alopecia (“lupus hair”) is sometimes encountered in CLE but often remains underdiagnosed. Scarring alopecia is a symptom of DLE involving the scalp. The presence of Raynaud’s phenomenon, calcinosis cutis, scleroderma-like changes, or rheumatoid nodules in patients with LE points towards an overlap syndrome.
Dermatomyositis

Involvement of the skin is an essential criterion for the diagnosis of dermatomyositis (DM).\(^{33, 34}\) Importantly, skin manifestations may precede the clinical symptoms of myopathy (muscle weakness, muscle pain, electromyopathic abnormalities or increased levels of creatine phosphokinase) in about 1/3 of patients with DM. In 10-20% of all patients with DM-specific skin changes occur longer than 6 months before systemic involvement (DM *sine* myositis or amyopathic DM).

The heliotrope rash is the most commonly encountered specific skin sign of DM (Figure 10). It consists of a violaceous, confluent erythema resembling the colour of the heliotrope, a red/purple-coloured flower tracking the course of the sun. The heliotrope rash of DM has a characteristic distribution involving especially the periorbital area. Patients often complain of a burning sensation but photosensitivity is rarely recognized. Other sites of this rash are the malar area of the face, the posterior neck and shoulders (referred to as “shawl sign”) and the scalp. Moreover, DM very often involves the extensor surfaces of the extremities, the knuckles and the dorsal aspects of the interphalangeal joints and the periungual area of the fingers in a symmetric fashion (Figure 11). In contrast to distributed ACLE lesions the dorsal finger sites between the interphalangeal joints are often spared. Moreover, violaceous colour and the periorbital distribution of the heliotrope rash distinguish DM from the malar rash in patients with ACLE.

If left untreated early DM lesions develop into plaques covered with a fine silvery scale especially on the knees and elbows. Once encountered on the knuckles, interphalangeal joints and in the periungual area they are called Gottron’s papules (Figure 11) while violaceous macules developing over the knuckles and the elbows and/or knees are known as the Gottron’s sign (Figure 12). Occasionally inflamed skin lesions of DM may develop into erosions, subepidermal blisters and ulcers (Figure 13). Less frequently patients with DM may develop poikiloderma atrophicans vasculare, a combination of violaceous erythema, hyperpigmentation, hypopigmentation, telangiectasia and atrophy.

In addition to these specific skin signs patients with DM may suffer from non-specific skin signs including nail fold telangiectasias (Figure 14) and dystrophic (“ragged”) cuticles. The mucosal membranes

![Figure 10.—DM with heliotrope rash.](image)

![Figure 11.—Gottron’s papules in DM.](image)

![Figure 12.—Gottron’s sign in DM.](image)
which are highly specific for DM and polymyositis but do not occur in other connective tissue diseases. However, the precise role of these antibodies in eliciting the characteristic skin manifestations of DM is unknown. Activation of complement cascades leading to formation and deposition of the mem-
embranolytic attack complex in endomysial capillaries has been implicated in muscle ischemia and destruc-
tion although the specificity of these events in DM has been recently set under question.

Histopathology of the heliotrope erythema reveals an interface dermatitis with a sparse lymphocytic infiltrate, epidermal atrophy, vacuolar alteration of the basal keratinocytes, basement membrane degeneration, and interstitially deposited mucin. More advanced lesions demonstrate lichenoid infiltrates consisting mainly of CD8+ lymphocytes and acanthosis of the epidermis.

The differential diagnoses of DM include SLE, psoriasis, atopic dermatitis, photoallergic- and -toxic drug eruption, contact dermatitis, cutaneous T-cell lymphoma, systemic sclerosis and trichinosis.

Systemic sclerosis

Sclerosis describes an induration of tissue due to an altered extracellular matrix turnover, especially collagen type I, which resembles fibrosis. Indeed, sclerosis cannot be considered a specific skin sign of systemic sclerosis (SS) since several other dis-
features.
Definition a multisystem disorder involving the skin plus internal organs often associated with a typical serological antinuclear antibody profile. Clinically, the extent of sclerosis of the skin can be easily assessed by the modified Rodnan skin score (mRSS), although its sensitivity for detecting small but clinically significant changes has been questioned.45 Alternative but less routinely used tools are 25 MHz ultrasonography and the durometer device.

There is striking heterogeneity within the clinical spectrum of cutaneous thickening in patients with SS. Two main subtypes of SS with distinct clinical and prognostic features have been identified. In patients with diffuse SS, skin thickening involves the trunk and proximal portions of the extremities while in patients with limited SS, the skin induration is confined to the face and distal portions of the extremities. However, in many cases overlaps exist between these two widely accepted clinical forms of SS. Recent studies correlate severity and course of skin fibrosis with overall prognosis.46 Furthermore, an evaluation of 1200 patients enrolled in the German Systemic Sclerosis Network showed that patients with increased mRSS have a higher prevalence of dysphagia, pulmonary fibrosis, reflux, digital ulcers and joint contractures, but not other systemic complications.47 A subtype of the limited form SS with induration of the fingers (“sclerodactyly”) is CREST (Calcinosis, Raynaud’s phenomenon, Esophageal hypomotility, Sclerodactyly, Telangiectasia) syndrome. These patients typically have detectable anticientromer antibodies and an overall favourable prognosis compared with patients suffering from diffuse SS. Finally, scleroderma sine scleroderma is a rarely encountered entity, in which affected patients have evidence for SS due to SS-related antibodies and internal organ involvement but no skin involvement. The prognosis of these patients appears similar to those with limited SS.

The majority of patients with SS recall Raynaud’s phenomenon many years before the onset of skin induration (Figure 15). Albeit a non-specific sign which is seen in patients with other connective tissue diseases Raynaud’s phenomenon is present in 90-99% of patients with diffuse or limited SS. When cutaneous involvement proceeds there is often an edematous phase of the affected skin areas, especially on the fingers (“puffy fingers”) (Figure 16). Similar changes can occur on the forearms, legs, feet, face and trunk. This is followed by thickening of the skin

Figure 15.—Raynaud’s phenomenon in SS.

Figure 16.—Puffy fingers in SS.

Figure 17.—Sclerodactyly in SS.
These telangiectasias are most often located in the face including the lips but may also be present on the neck, volar aspects of the fingers and palms (Figure 19). Another helpful skin sign of SS are dilated nail fold capillaries, often alternating with areas of loss of capillaries. They can be easily assessed by dermatoscopy or in more detail by nail fold capillary microscopy. Calcinosis a further key feature of CREST syndrome. It tends to be located on the extremities, especially at the finger tips and over joints (Figure 20).

Diffuse hyperpigmentation of the skin is not a rare phenomenon in patients with SS. However, its role as a potential indicator of disease severity and/or prognosis remains unknown. It mostly occurs as a diffuse brownish discoloration resembling a sun tan. In other patients with SS a combination of hyper- and hypopigmentation (“salt and pepper”) may develop especially on the upper trunk.

The pathogenesis of SS is incompletely understood. However, recent advances in our knowledge on the molecular mechanisms of fibrosis have shed more light into this fascinating field of research. Many investigators believe that endothelial cell damage is crucial in initiating an inflammatory response that subsequently leads to the fibrotic stage of the disease.48 In early disease, vascular injury may lead to tissue hypoxia which triggers the induction of several proinflammatory cytokines including transforming growth factor-β1 (TGF-β1).49, 50 TGF-β1 is considered a master regulator of collagen metabolism and a key profibrotic cytokine that upregulates collagen synthesis in dermal fibroblasts at the transcriptional and
non-transcriptional level. Ex vivo studies on dermal fibroblasts from patients with SS as well as in situ studies on lesional skin of SS have unravelled alterations in TGF-β1 function and/or canonical TGF-β1 signalling including the transcription factor Smad. In addition, expression of non-Smad signal transduction intermediates, e.g. the immediate-earliest response transcription factor EGR-1, have been found to be stunted in SS. Other cytokines such as endothelin-1 and hepatocyte growth factor appear to be involved in the development of diffuse hyperpigmentation but also of vascular alterations in patients with SS. Recent studies have implicated a pathological activation of the morphogenic pathways Wnt, Hedgehog and Notch, key regulators of organ development and tissue homeostasis, in this chronic disease stadium. In experimental fibrosis models, activation of these pathways induced collagen type I synthesis, transdifferentiation into myofibroblasts and tissue fibrosis while their blockade could inhibit these effects. Specifically, β-catenin is a key pro-fibrotic mediator of the canonical Wnt pathway in SS and its modulation could be of novel therapeutic relevance. Furthermore, a decrease in PPAR-γ, an endogenous anti-fibrotic mediator, has been identified in a subset of SS patients and may further abrogate fibrosis.

There is recent evidence that distinct neuroendocrine pathways are also involved in the pathogenesis of SS and/or may be exploited as future therapies against this disease. Serotonin (5-hydroxytryptophan, 5-HT) has long been speculated to contribute to Raynaud’s phenomenon in patients with SS but only recently its role as a direct fibrotic mediator has been elucidated in more detail. Being stored in platelets but released upon activation of these cells it directly acts via 5-HT2B receptors in fibroblasts and promotes tissue fibrosis. Pharmacological blockage of 5-HT2B receptors ameliorated experimentally induced fibrosis. In addition, endocannabinoids seem to have a stimulatory effect on cutaneous fibrosis via signalling of the cannabinoid receptor CB1 while the cannabinoid receptor CB2 seems to mediate antifibrotic effects. On the other hand, neuroendocrine pathways exist which act in an antifibrotic direction and which include melancortin peptides and agonists of the α7 nicotinic acetylcholine receptor (α7nAchR). Our own laboratory could demonstrate that α-melanocyte-stimulating hormone (α-MSH), a prototype of melancortin peptides, antagonizes TGF-β1-mediated collagen type I synthesis in vitro and in vivo. In the bleomycin mouse model of SS α-MSH also attenuated skin fibrosis presumably via antioxidative pathways. Interestingly, a functionally active melancortin 1 receptor (MC1) binding α-MSH and related peptides protects from bleomycin-induced fibrosis in mice. In this context it is interesting to note that insufficient MC1 expression and signalling has been noted in keloids suggesting that α-MSH-mediated pathways may also be disturbed in SS. In addition, we could recently demonstrate that targeting the α7nAch, e.g. by tropisetron, directly attenuates TGF-β1-mediated fibroblast activation. In vivo treatment with this agent not only suppressed experimentally induced skin fibrosis but also had an antifibrotic effect.

With regard to autoantibody production in SS the precise pathogenetic role of anti-topoisomerase and anti-centromere antibodies still remains unclear. In addition to the presence of the former autoantibodies anti-fibroblast antibodies have been detected in 46% of SS patients. They were found to be internalized into dermal fibroblasts and induce a proadhesive and proinflammatory cellular phenotype. Moreover, antibodies against endothelial cells and PDGF receptors may lead to endothelial cell activation and tissue damage. On the genetic level, micro-array based genome-wide expression profiling in skin biopsies from SS patients identified more than 2000 genes with altered expression in SS. Both HLA- and non-HLA-genes have been identified. Finally, epigenetic mechanisms, e.g. DNA methylation, histone modification and altered miRNA expression have been displayed in SS. Differential miRNA expression profiles in diffuse and localized disease underline the potential role of these as biomarkers in SS. MiRNAs seem to induce or attenuate fibrosis by targeting the canonical TGF-β1/Smad pathway.

Finally, adaptive and innate immunity pathways seem to play an important role in SS pathogenesis. In initial stages, perivascular mononuclear cells secrete profibrotic cytokines and chemokines. Furthermore, an imbalance of Th1 and Th2 cytokines with shift towards Th2 cytokines seems to promote fibrosis. Finally, type I IFN pathways and activation of TLRs are implicated in pathogenesis of SS. Histopathology of sclerotic skin from patients with SS typically shows excessive collagen deposits within the dermis and subcutaneous tissue. Adnexal structures are often entrapped. In early lesions (oede-
matous phase) a dense lymphocytic infiltrate is seen at the interface of the deep dermis and adipose tissue.

The differential diagnosis of SS includes scleromyxedema, eosinophilic fasciitis (Shulman syndrome), scleredema adultorum and diabeti- corum, diabetic thick skin, sclerosizing chronic graft-versus-host disease, sclerosizing forms of porphyria, POEMS syndrome, nephrogenic fibrosing dermopathy, eosinophilic 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’s syndrome**

Mucocutaneous symptoms are often the leading clinical symptom in patients with Sjögren’s syndrome (SjS), also known as Mikulicz disease, or sicca syndrome, a systemic autoimmune disorder primarily affecting the salivary glands. SjS primarily affects women, with a female to male ratio of 9:1. The disease may present alone as primary SjS or as secondary SjS in the context of almost every other autoimmune disease. Compared with the former major connective tissue diseases CLE and dermatomyositis there are no specific skin lesions. Upon histopathology of affected salivary glands a lymphocytic infiltration including mononuclear cells, T- and B-lymphocytes is seen. Although a non-specific 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 may not only involve the mouth (xerostomia, eyes leading to keratoconjunctivitis sicca, Figure 21), but also the vagina. Patients typically complain of dryness and soreness with burning sensations. Vaginal xerosis may result in dryness, burning and dyspareunia. Due to diminished salivary production angular stomatitis (Perleche) is common. Surprisingly, increased awareness and dental care does not lead to a higher incidence of dental and gingival problems in patients with SjS.

The pathogenesis of the mucocutaneous changes in patients with SjS is incompletely understood, however immune-mediated and not immune-mediated mechanisms seem to be involved. A widely accepted model of pathogenesis of SjS suggests that in genetic predisposed individuals environmental factors such as viral infections may cause epithelial cell activation, which leads to induction of proinflammatory pathways, infiltration of immune cells and subsequently glandular dysfunction.

A genetic disposition is suggested by the increased prevalence of specific HLA-haplotypes. Among them, HLA-DR5 was also related to the presence of anti-Ro and anti-La antibodies. Non HLA-gene polymorphisms such as STAT-4, IL-12A, TNIP-1, IRF-5, BLK and CXCR-5 seem also to mediate a predisposition to disease. Furthermore epigenetic mechanisms including defective DNA methylation and altered miRNA expression has been shown to modulate gene expression and the inflammatory response in SjS. Interestingly, viruses have for a long time been considered as potential triggers for the immune response in SjS. Some reports have found an association between SjS and HTLV-1, Epstein-Barr virus, human immunodeficiency virus and hepatitis C virus. Viral infections may trigger epithelial activation via binding to TLRs. Recently, TLR 3 activation and induction of type I interferon pathways have been identified in early SjS stages and seem to play a decisive role in immune attack and dysfunction of glandular tissues.

As demonstrated by the histopathologic picture of specimens from minor salivary glands the interaction between lymphocytes and salivary gland epithelia appears to in the centre of the pathogenesis of SjS. The term “epithelitis” has been created to describe an epithelial cell activation leading to aberrant expression of molecules crucial for lymphocyte...
recruitment and activation thereby resulting in apoptosis of salivary gland epithelia in patients with SjS. Apoptosis in epithelial cells in SjS may occur in a Fas/Fas ligand-dependent pathway or after direct interaction with cytotoxic T-lymphocytes. Apoptosis of epithelial cells leads to release of cellular constituents, which are recognised from antigen presenting cells, further potentiating activation of T- and B-lymphocytes.

Periductal immune cell infiltrates in SjS consist of activated T- and B-cells, macrophages and dendritic cells. The infiltrating lymphocytes show elevated levels of the apoptotic regulators bcl-2 and bcl-x which may favour increased survival of the cells and eventually development of marginal B-cell lymphoma in the salivary glands. Moreover abnormal expression of B-cell activating factor (BAFF) from monocytes and epithelial cells, as well as of its receptor promote B-cell survival and are related to lymphoproliferative complications such as B-cell lymphoma in SjS patients.

The female predominance points to sex specific predisposing factors, and recently evidence is accumulating about the role of estrogens in autoimmunity. Androgens seem on the other hand to be protective. An imbalance of the androgen/estrogen ratio has been discussed in pathogenesis of SjS, as peak age of the disease is the premenopausal period. Low systemic and salivary levels of dehydroepiandrosterone (DHEA) and its metabolite DHEA sulfate (DHEA-S) have been observed in SjS.

It is well known that patients have positive anti-Ro (30-95%) and anti-La (15-60%) antibodies but their precise role in the pathogenesis of the disease remains unknown. Furthermore, autoantibodies against muscarinic receptors have been identified in up to 90% of patients with SjS. These could lead to autonomic nervous system dysfunction and thus contribute to xerostomia and xerophthalmia in SjS, although their exact role remains controversial.

In addition to the afore-mentioned key signs of the mucous membranes there other non-specific skin manifestations that frequently occur in patients with SjS. Xerosis cutis is present in 50% of SjS patients and may lead to generalized pruritus. Another frequent sign is palpable and non-palpable purpura often located on the legs (Figure 22). It is typically induced or aggravated by physical exertion. Additional forms of cutaneous vasculitis in patients with SjS include lymphocytic vasculitis, and urticarial vasculitis (either hypocomplementemic or less commonly normocomplementemic). By definition, 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. Lesions often heal with hyperpigmentation. Upon histology, there is a mononuclear cell infiltration with disruption of the architecture of the small blood vessels.

Other systemic rheumatic diseases

Rheumatoid arthritis

Rheumatoid arthritis (RA) is often associated with skin changes. They can be RA-specific, non-specific
or associated skin diseases. Rheumatoid nodules and nodulosis, accelerated rheumatoid nodulosis, rheumatoid neutrophilic dermatosis and rheumatoid vasculitis are considered RA-specific skin manifestations.

Rheumatoid nodules (RN) are the most commonly encountered extra-articular manifestation of patients with RA. About 25% of RA patients develop these lesions. They are more frequent in white males and in patients with rheumatoid factor (RF)-positive RA. Patients with an HLA-DR4 haplotype and those with heterozygosity for HLA-DRB1 are at increased high risk for rheumatoid nodules. Clinically, RN are subcutaneous, firm, and painless papules or nodes measuring from a few mm to some cm in size. Predilection sites are the periarticular regions of the extensor surfaces of the fingers. At the histological level, RN consist of palisading macrophages around an area of central collagen degeneration, surrounded by an area of perivascular T-lymphocytes, plasma cells and macrophages. The pathogenesis of RN remains obscure. Recent studies suggest endothelial damage at areas prone to mechanical trauma leading to immune complex aggregation and focal vasculitis, Th1-cytokines like TNF-α and IL-1β as well as macrophage chemotaxis and activation in RN formation. Complications include infection, ulceration, gangrene, bursitis and synovial rupture. RN must be differentiated from chronic tophaceous gouty arthritis, rheumatic fever nodules, subcutaneous nodules found in systemic lupus erythematosus, nodular or keloidal scleroderma, as well as nodules seen in necrobiosis lipoidica and granuloma annulare. In addition, tumoral calcinosis, fibromas, xanthomas, subcutaneous sarcoidosis, metastatic tumors, amyloidosis, ganglion cysts, foreign body granuloma, basal cell carcinoma, epidermoid cysts and synovial cysts must be executed.

Rheumatoid nodulosis is characterized by multiple subcutaneous rheumatoid nodules, recurrent joint symptoms, frequently cystic involvement of small bones and no or mild systemic manifestations of RA. The disease usually is self-limited and well controlled by non-steroidal anti-inflammatory drugs.

Accelerated rheumatoid nodulosis was initially reported in patients treated with methotrexate (MTX) for RA or juvenile RA. Affected patients develop painful nodules mainly on the hands (Figure 23). RA patients receiving in addition to MTX hydroxychloroquine, D-penicillamine, colchicine, and sulfasalazine did not develop accelerated rheumatoid nodulosis. Similar nodules have been observed in a patient with psoriatic arthritis during MTX challenging the view that accelerated rheumatoid nodulosis is RA-specific. Recently, accelerated rheumatoid nodulosis also has been described in patients receiving etanercept. Mechanistic studies revealed that MTX enhances multinucleated giant cell formation in monocytes in an adenosine-1 receptor-dependent pathway. Blockade of this pathway by colchicine led to regression of nodulosis in vitro and in vivo.

Rheumatoid neutrophilic dermatosis is also regarded as a rare but RA-specific skin sign. Patients with severe and seropositive RA appear to be affected. It manifests with asymptomatic erythematous urticarial papules and plaques. Ulceration is possible. Lesions are typically located on the forearms and hands.

Rheumatoid vasculitis is regarded as a late complication of RA. It may not only involve skin but also internal organs and is thus a potentially life-threatening extra-articular manifestation of RA. In the skin it can result in a variety of cutaneous skin signs (Table II). It mostly occurs in seropositive and mainly male patients with longstanding RA and is often associated with presence of autoantibodies against citrullinated peptides. If small vessels are affected there are palpable and non-palpable purpura, localized petechiae, splinter hemorrhages, nail fold infarctions (Bywaters lesions), and peripheral neuropathy. If medium-sized vessels are affected cutaneous findings include nodules, ulcerations, livedo..
There is a large number of non-specific skin signs and associated skin diseases in patients with RA (Table III). Pyoderma gangrenosum (PG) is commonly associated with RA both in RF-positive and negative patients. Lesions start as a tender erythematous or violaceous papule and rapidly expand into a hemorrhagic or purulent necrotic ulcer with ragged edematous edges (Figure 24). Lesions are painful and are most often located on the lower extremities. The Koebner and pathergy phenomena are positive. Since PG does not only occur in RA chronic relaps-
leukocytoclasis, histiocytes, and lymphocytes and sometimes eosinophils are present. Like PG and Winkelmann’s disease interstitial granulomatous dermatitis occurs in other autoimmune disorders than RA and also neoplastic diseases. It must be also distinguished from granulomatous diseases including granuloma annulare, necrobiosis lipoidica, granulomatous slack skin and interstitial granulomatous drug reactions.

The recent years have witnessed major advances in the understanding of the pathogenesis of RA which also broadens our insight into skin manifestations of the disease. Macrophages as well as resident joint cells including synovial fibroblasts are considered to be major effectors of synovial inflammation, secreting proinflammatory cytokines including TNF-α, IL-1 and IL-6 as well matrix degrading enzymes. Activation of autoreactive T-cells and suppression of Tregs further promote inflammation. B-lymphocytes contribute to RA progression through production of proinflammatory cytokines and generation of autoantibodies characteristic of disease.

Although the presence of RF and its value in predicting the development of the disease have been early recognised in patients with RA it remains unclear if this molecule plays an active role in disease pathogenesis. RFs are autoantibodies against the Fc fraction of immunoglobulins. Anti-citrullinated protein antibodies have been also recently recognised as important diagnostic markers of RA. Recent genome-wide association studies have revealed around hundred associated genetic loci. The best established genetic association with RF-positive RA is the “shared epitope” MCH class II alleles. A deficient epigenetic control, specifically a reduced DNA methylation, is found in RA synovial fibroblasts. Moreover, altered expression of miRNA seems also to modulate inflammation in the posttranslational level in patients with RA.

In experimental murine arthritis models, there is an emerging role of endosomal TLRs (TLR-3, -7, -8 and -9) which recognise self and foreign nucleic acid structures, in pathogenesis of RA.

Systemic onset juvenile rheumatoid arthritis

Systemic onset juvenile rheumatoid arthritis is also called juvenile rheumatoid arthritis, juvenile chronic arthritis, and Still’s disease.

Since skin manifestations can precede arthralgias
in patients with systemic onset juvenile rheumatoid arthritis (SOJRA) for years knowledge of these signs is important for both dermatologists and rheumatologists to make an early diagnosis. There are two clinical variants of SOJRA. In the acute onset febrile systemic 90% of the patients develop a non-pruritic transient exanthema that recurs with fevers. Lesions consist of a pinkish macular or maculopapular rash distributed over the trunk. Koebnerization is common. Histopathology reveals a discrete perivascular mixed infiltrate with edema of the upper dermis. In the chronic oligoarticular variant of SOJRA with low-grade persistant fever rheumatoid nodule-like lesions may develop. They have a predilection for the extensor surfaces of the extremities and can be both clinically and histologically indistinguishable from those of RA patients.

In the last decade important steps in understanding the pathogenesis of SOJRA have been made. Elevated levels of IL-6, IL-1β and IL-18 as well as the marked effects of anti-IL-1 and anti-IL-6 strategies in disease control indicate that these cytokines are important players in its pathogenesis. It was shown that serum from patients with SOJRA can induce release of various IL-1-related genes in peripheral blood mononuclear cells of control patients. In addition, polymorphisms in the IL-6 gene promoter, leading to changes in IL-6 levels have been identified and may confer a genetic predisposition to the disease. Finally various circulating autoantibodies have been detected in patients with SOJRA but it is unclear whether these observations are of pathogenetic relevance or represent an epiphenomenon.

The typical exanthema of SOJRA in combination with fever and arthralgias must be distinguished from 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.

**Adult onset Still’s disease**

Adult onset Still’s disease (AOSD) is a rare multi-systemic inflammatory disease which is today considered as a polygenic autoinflammatory syndrome. Clinical features include high fever, neutrophilic leukocytosis, arthralgias and skin rash. Patients may also develop sore throat, myalgias, generalized lymphadenopathy, hepatosplenomegaly, pleuritis and pericarditis. Laboratory examinations reveal a systemic inflammatory constellation with increased C-reactive protein, erythrocyte sedimentation rate and ferritin. Based on clinical presentation, two subtypes may be distinguished. In the first variant systemic symptoms with fever prevail while in the second arthritis is the leading symptom without systemic symptoms. The disease affects usually young adults with a predominance of women. Viral or bacterial infections have been proposed to trigger the disease. Moreover an association with malignancies, mainly solid cancers of breast and lung as well as hematologic malignancies has been reported. Due to unspecific systemic manifestation and the wide range of differential diagnoses definitive diagnosis of AOSD is difficult. Of the various proposed diagnostic criteria these of Yamaguchi or Fautrel are today most widely used.

The typical skin manifestation of AOSD is a salmon-pink, maculopapular exanthema predominantly affecting the proximal extremities and trunk. Lesions characteristically appear during fever spikes and resolve with resolution of fever. Persistent pruritic papules and plaques are another skin sign of AOSD, characterized by slight scaly papules and plaques with a linear configuration on the trunk. Furthermore, patients have typically an urticarial dermatographism.

Histopathology of the typical skin lesions reveals a mild inflammatory infiltrate of mononuclear leukocytes and neutrophils in the upper dermis. Biopsies of persistent pruritic papules and plaques show on the contrary specific histological features, including dyskeratotic keratinocytes on the upper epidermal layers and areas with focal hyperkeratosis.

The exact pathogenesis of the disease remains unclear. Recent reports underline the role of NLRP3 inflammasome activation, leading to production of IL-1β and IL-18 and initiating a Th1 inflammatory response. This results in activation of macrophages and neutrophils, which is the hallmark of the disease. Interestingly, elevated levels of TNF-α, IL-1β, IL-6, IFN-γ have been identified in serum of affected patients. IL-6 is considered as the major cytokine leading to liver synthesis and release of ferritin. Finally, specific HLA alleles as well as polymorphisms in the IL-18 gene may confer a genetic susceptibility for the disease.
Relapsing polychondritis (Atrophic polychondritis, systemic chondromalacia, polychondropathia)

Relapsing polychondritis (RP) is a chronic inflammatory multisystem disorder leading to significant morbidity due to destruction of the cartilaginous tissue in many organs. Importantly, cutaneous involvement is the first clinical sign in many patients with RP.

The most specific skin sign of RP consists of erythema, swelling, and pain of the cartilaginous part of the ear. The earlobe is most characteristically spared (Figure 26). The majority of RP patients suffer from such auricular involvement during the course of their disease. If left untreated persistent inflammation of the outer ear will lead to destruction of the auricular cartilage (“cauliflower ears”). If RP involves nasal cartilage nose deformity may result (“saddle nose deformity”).

The presence of autoantibodies recognising the cartilage matrix proteins type II collagen and matrilin-1 implicates an autoimmune process in the pathogenesis of RP. The association with MHC Class II alleles, among them HLA-DR4, HLA-DQA1 and HLA-DQB1 also suggests an immunologic mechanism responsible for the destruction of cartilaginous tissue.

Today it is believed that various noxa, such as trauma and infections, may lead to exposure of connective tissue self-epitopes in predisposed individuals and trigger an aberrant immune response. Key effector cells of tissue destruction are macrophages and neutrophils via production of matrix metalloproteinases, elastases and reactive oxygen species. Increased cytokine- and chemokine-levels, such as MCP-1, IL-8, TNF-α and IFN-gamma further amplify and sustain the inflammatory response.

At the histological level, inflamed cartilage shows a loss of its basophilic staining due to destruction of glycosaminoglycans and a pleomorphic infiltrate of macrophages, neutrophils, lymphocytes and plasma cells. At later stages the cartilage is replaced by granulation tissue and fibrosis.

About one third of patients with PR suffer from other non-specific signs. Since RP can be associated with other systemic diseases, e.g., myelodysplastic syndromes, Behçet’s disease or an underlying neoplasm it is often difficult to attribute these skin changes to RP per se. Moreover, some of these skin signs may be related to systemic treatment. Various forms of vasculitis including palpable purpura, livedo reticularis and erythema elevatum et diutinum, non-inflammatory vasculopathies such as livedo reticularis, panniculitis, and aphthosis (oral or complex) have been observed in patients with RP.

The differential diagnosis of painful erythema and swelling in the context of RP must be distinguished from physical trauma, erysipelas and Wegener’s granulomatosis, the latter which can also result in cartilage destruction especially of the nose.

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Cutaneous signs of classical dermatomyositis

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Idiopathic immune myopathies (IIM) are an heterogeneous group of autoimmune muscle disorders characterized by progressive muscle involvement. Dermatomyositis (DM) is the most common form of IIM. It is a multisystem disorder characterized by symmetric proximal, extensor, inflammatory myopathy, vascular involvement and a characteristic cutaneous eruption. Six types of DM have been identified: idiopathic, juvenile (JDM), cancer-related other autoimmune diseases-related, iatrogenic DM and amyopathic DM. Cutaneous manifestations of DM are the most important aspect of this disease and can precede from several months to years muscle or systemic involvement. Three groups of signs have been described: pathognomonic, highly characteristic and compatible. Although differences exist among the different clinical presentation of skin lesions, they share common histological findings including the presence of interface dermatitis with epidermal atrophy, basement membrane degeneration, vascular alteration of basal keratinocytes, and dermal changes consisting of interstitial mucin deposition and a sparse lymphocytic infiltrate. DM is a serious disease; the correct evaluation of any skin lesion suggesting an early diagnosis is of utmost importance. Skin signs may, also, represent a marker of treatment efficacy even though systemic symptoms worsening may not always be followed by more severe skin lesions.

KEY WORDS: Dermatomyositis - Skin manifestations - Muscular diseases.

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of IIM. It is a multisystem disorder characterized by symmetric proximal, extensor, inflammatory myopathy, vascular involvement and a characteristic cutaneous eruption. The pathogenesis of this disease is still under investigation however several trigger factors have been identified including: infections (e.g. HIV, EBV, HBV), drugs (e.g. anti-TNF), and environmental factors (especially ultra-violet radiations [UV-r]); instead no correlations have been proposed with vaccinations.2

Six types of DM have been identified (Table I): idiopathic, juvenile (JDM), associated to cancer (paraneplastic), associated to other autoimmune diseases (overlap syndromes), iatrogenic DM, and amyopathic DM (ADM).

DM may affect both children and adults. Children under 18 years of age (JDM) and adults between 40-60 year old are more frequently affected. The overall female/male ratio for the classical form of DM is about 2:1.3

Paraneoplastic DM usually develops in older patients (45-74 years old).1,4 Its frequency is very variable, since it has been described in 6-60% of DM cases.5 The development of cancer usually follows DM presentation in almost two thirds of cases. Thus the early recognition of cutaneous DM signs is very important.

AMD is usually described as the presence of typi-
Cutaneous signs of classical dermatomyositis cutaneous signs without any sign of muscular disease for at least 6 months.

**Clinical symptoms**

DM diagnostic criteria have been established by Bohan and Peter in 1975 \(^6\), \(^7\) and include: symmetric proximal muscle weakness, elevation of serum skeletal muscle enzymes (CK) and lactate dehydrogenase (LDH); electromyographic specific signs; muscle biopsy abnormalities and typical skin rash of DM.

Muscular symptoms are characterized by weakness and myalgia of the proximal limbs, a decrease of strength in the proximal muscles associated to contractures leading to muscular atrophy, respiratory and oro-pharyngeal muscle involvement causing dysphagia, respiratory difficulties and ab-ingesis pneumonia.\(^8\) Muscle’s disease activity is frequently discordant from skin lesions presentation,\(^9\) thus DM diagnosis can be challenging when muscle weakness is not obvious or missing and when skin lesions are similar to other autoimmune connective tissue diseases.\(^10\)

Systemic symptoms and involvement of other organs may also be present such as: fever, malaise, weight loss, arthralgias, interstitial lung disease and cardiac dysfunction. Elevation of CK levels, which is indicative of muscle damage, is the most sensitive enzyme test and usually parallel disease activity so, CK levels, can be used to monitor DM therapy response. Muscle biopsies and electromyography can be used as confirmatory tests; beside, noninvasive diagnostic procedures such as magnetic resonance imaging and ultrasound are helpful in finding muscle inflammatory lesions.\(^10\)

Cutaneous signs may precede muscular involvement by several months or years and have been classified in: pathognomonic, highly characteristic and DM compatible skin lesions.\(^11\)

**Cutaneous manifestations of DM**

Cutaneous manifestations of DM are the most important aspect of this disease, being the hallmark of disease definition and diagnosis; moreover they are consistent throughout the various subtypes of disease. Skin signs can proceed of several months to years, muscle or systemic involvement.

DM skin signs are important since they lead to early recognition of the disease; this in turn favors an early treatment and strict follow-up to improve patient quality of life (QoL). In fact, skin lesions reduce QoL in DM patients.\(^12\) However, skin lesions, are not always simultaneous to DM systemic symptoms or they may appear as atypical presentations. Skin lesions identification is of ultimate importance in paraneoplastic and amyopathic DM to ensure a higher and better life expectancy. Skin signs of DM are not always easily recognizable. Classical skin DM signs like malar erythema and Gottron’s papulae may assume atypical aspects. These atypical manifestations may present concomitantly to less frequent but specific signs of DM like cuticular hyperkeratosis, periungual erythema, the “V sign” (presence of erythemato-violaceous skin in the upper chest and anterior neck), the “Shawl sign” (the presence of poikilodermic skin on the shoulders and upper back), the “Holster sign” (the presence of poikilodermic skin on the antero-lateral aspects of thigs), non scarring alopecia, hyperkeratotic lesions on the hands (mechanic’s hands), and oral erosions. The association of these lesions may characterize specific clinical presentation of DM associated to autoantibody. Here follows the description of some unusual presentation of classical skin DM signs and the more frequent non-specific lesions associated to DM.

Three groups of signs have been described: 1) pathognomonic (typical of DM); 2) highly characteristic (which may suggest the diagnosis of DM); and 3) compatible (which may be present in DM). Most of the lesions appear in sun-exposed areas since DM is classically defined as a photoaggravated disease.

**Pathognomonic DM lesions**

Gottron’s papules, together with Gottron’s sign represent the pathognomonic DM lesions, present in almost 70% of patients.\(^13\)

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**Table I.—Classification of the different DM types.**

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\(^6\) Bohan A, Peter JB. 1975. Symptomatic proximal muscle weakness, elevation of serum skeletal muscle enzymes (CK) and lactate dehydrogenase (LDH); electromyographic specific signs; muscle biopsy abnormalities and typical skin rash of DM.

\(^7\) Bohan A, Peter JB. 1975. Symptomatic proximal muscle weakness, elevation of serum skeletal muscle enzymes (CK) and lactate dehydrogenase (LDH); electromyographic specific signs; muscle biopsy abnormalities and typical skin rash of DM.

\(^8\) Muscle’s disease activity is frequently discordant from skin lesions presentation.

\(^9\) Thus DM diagnosis can be challenging when muscle weakness is not obvious or missing and when skin lesions are similar to other autoimmune connective tissue diseases.

\(^10\) Systemic symptoms and involvement of other organs may also be present such as: fever, malaise, weight loss, arthralgias, interstitial lung disease and cardiac dysfunction.

\(^11\) The association of these lesions may characterize specific clinical presentation of DM associated to autoantibody. Here follows the description of some unusual presentation of classical skin DM signs and the more frequent non-specific lesions associated to DM.

\(^12\) Skin lesions reduce QoL in DM patients.

\(^13\) Gottron’s papules, together with Gottron’s sign represent the pathognomonic DM lesions, present in almost 70% of patients.
Gottron’s papules

Gottron’s papules consist of violaceous slightly scaly papules and plaques symmetrically found over bony prominences, particularly over the metacarpophalangeal, proximal interphalangeal and/or the distal interphalangeal joints (Figure 1). However they can be found also over other joints (elbows and knees). In late stages Gottron’s papules can be characterized by the presence of telangiectasias, hypopigmentation, ulceration (Figure 2).8, 14, 15 Active lesions tend to resolve with dyspigmentation, atrophy, and scarring.16 Sometimes hyperkeratosis may be present resembling psoriasis lesions (Figure 3).

Gottron’s sign

Gottron’s sign is a symmetrical macular violaceous erythema with or without edema overlying the dorsal aspect of the inter-phalangeal or metacarpophalangeal joints (Figure 4), olecranon processes, patellae, and medial malleoli.

Heliotrope rash

Heliotrope rash is a lilac discoloration or a violaceous to dusky erythematous rash in a symmetric distribution involving the periorbital skin (Figures 5, 8, 14, 15).
AURIELEMA

CUTANEOUS SIGNS OF CLASSICAL DERMATOMYOSITIS

6), which is also considered a pathognomonic sign of DM. The term heliotrope refers to the purplish color of the petals of the flower Heliotropium peru-vianum. Edema and telangiectasia may accompany the rash or be present in a late stage sign (Figure 7). Usually the Heliotrope rash spares the nasolabial folds (Figure 8). However a more widespread erythema can affect the perioral area, the forehead, and the lateral face and ears. In those cases, erythema often involves the cartilaginous portion of the helix of the ear, sparing of the earlobe. In rare cases, the rash may consist in discrete areas of erythema (Figure 9). In darker skin types this erythema may be subtle and overlooked, and itch, pain or a burning sensation

Figure 5.—Heliotrope rash.

Figure 6.—Heliotrope rash.

Figure 7.—Heliotrope rash with telangiectasia.

Figure 8.—Heliotrope rash sparing the nasolabial folds.

Figure 9.—Heliotrope rash consisting in discrete areas of erythema.
may lead the diagnosis. All those lesions can evolve forming scales, crusts or ulcerations. The heliotrope rash can parallel the course of myositis and the intensification of the erythema may represent the first sign of a disease flare-up, suggesting the need for a further evaluation of systemic and muscular involvement.

**Nailfold erythema**

Erythema overlying the periungual areas is usually due to periungual telangiectasias which represent the dilated and tortuous “bushy capillaries” typical of DM capillaroscopy. This lesions are often associated with small hemorrhagic infarcts and cuticular hypertrophy (Figure 10). Periungual erythema is not pathognomonic of DM since may be present in other connective tissue diseases such as Lupus erythematosus and systemic scleroderma. The presence of this lesion parallels disease activity.

**Confluent macular areas of erythema**

This presentation may affect symmetrically the dorsal aspect of the hands like a macular violaceous erythema, or it can affect the extensor aspects of the arms and forearms and deltoids (Figure 11). Confluent erythema involving over 50% of the body surface area is rare in case of DM. Rarely, patients can present with a more ichthyotic variant of erythroderma, which appears as dry and cracked skin.

**DM compatible skin lesions**

**Poikilodermatous skin lesions**

Poikilodermatous skin lesions are characterized by telangiectasias, atrophy, depigmentation, and papules that can be observed on the dorsum of the hands and forearms, on the upper back (Figure 12) and posterior neck. They can be described as:

— **V sign:** erythematous lesions, which usually are followed by crusts and discolorations. Those lesions are present in a V shape around the anterior neck sparing non sun-exposed areas (Figure 13). The V signs is particularly present in patients with anti Mi-2 positivity.

— **Shawl sign:** it is characterized by the confluence of different grade of erythematous maculae with a specific distribution resembling a shawl distribution on the shoulders, posterior neck and on upper back; seldomly it involves the lateral aspects
AURIEMMA

CUTANEOUS SIGNS OF CLASSICAL DERMATOMYOSITIS

Figure 12.—Poikilodematous skin lesions.

Figure 13.—V sign.

Figure 14.—Shawl sign.

Figure 15.—Holster sign.

of the arms (Figure 14). The shawl sign, like the V sign, is associated to the presence of anti Mi-2 antibody, although in a lesser frequency.21

— Holster sign: it represents a simmetric erythema of skin of the thighs (Figures 15, 16). A similar erythema, called “Gottron’s sign” can be present on the skin overlaying the extensor tendons of hands, forearms, foots and legs.12 This sign is not DM specific; it can be, in fact, recognized in different immuno mediated dermatoses, although less frequently.18

SCALP INVOLVEMENT

Non-pathognomonic signs may be present on the scalp of DM patients frequently associated with disease flare up.14 A diffuse erythematous lilaceous macular presentation, presenting on the nuchal area (Figure 17) or a scaly psoriasis-like process may be present leading in some cases to moderate non-scarring alopecia (Figure 18).14 Usually these manifestation may be associated with very intense pruritus that is resistant to antihistaminic and corticosteroid therapy.18
CUTANEOUS SIGNS OF CLASSICAL DERMATOMYOSITIS

A URIEMMA

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Calcinosis, in the context of JDM, generally develops within a few years from diagnosis. Lesions are frequently located at sites exposed to trauma (e.g., knees, elbows, and buttocks). Four characterized patterns of calcinosis exist: cutaneous or subcutaneous plaques or nodules; deposits that extend to muscle; calcinosis cutis resulting in an ulcerative nodule with a surrounding erythematous skin.

Calcification can be present in the course of DM (Figure 19) especially in JDM. Usually calcinosis involves the skin, subcutaneous tissue, fascia, or muscle, consisting in tender, firm papules or nodules which can eventually ulcerate in the center and show a surrounding erythematous skin.

Calcinosis cutis

Calcification can be present in the course of DM (Figure 19) especially in JDM. Usually calcinosis involves the skin, subcutaneous tissue, fascia, or muscle, consisting in tender, firm papules or nodules which can eventually ulcerate in the center and show a surrounding erythematous skin.
along fascial planes that may lead to contractures, and widespread calcium deposition.\textsuperscript{23}

**EXCORIATIONS**

Pruritus is usually an accompanying symptom that can precede of several months the onset of skin or muscle symptoms. It usually determines excoriations and the development of linear streaks in the upper back (flagellate erythema – Figure 20). It represents one of the major stressor inducing a reduction in the quality of life (QoL) in DM patients.\textsuperscript{12}

**MECHANIC’S HANDS**

Mechanic’s hands consist in the presence of rough and cracked, hyperkeratotic, lichenoid lesion and papules on the lateral (Figure 21) and palmar areas of the fingers. Frequently such lesions are misinterpreted as eczematous lesions, however they are refractory to any form of topical treatment. These lesions may be associated with the presence of anti Jo-1 antibodies in particular subtypes of DM (t-istidil synthase syndrome).

**ORAL MANIFESTATIONS**

Oral manifestations consist in oral mucosal ulcers, white patches, and gingival telangiectasias and erythema as well as tongue involvement.\textsuperscript{24, 25} Xerostomia and salivary hypofunction can be found in the course of DM, eventually being the sign of a concomitant Sjögren Syndrome (SS).\textsuperscript{26}

**LIPODYSTROPHY**

Lipodystrophy is increasingly recognized in patients with JDM. Rarely seen at presentation, these changes develop later in the course of the disease in up to one-fourth of the patients.\textsuperscript{27}

**ULCERS**

Ulcers are serious manifestations of DM. These lesions presumably reflect significant vasculopathy in

![Figure 20.—Flagellate erythema.](image)

![Figure 21.—Mechanic’s hands.](image)
Particular DM subsets

CLASSICAL DM WITH MI-2 POSITIVE ANTIBODY

In case of anti Mi-2 antibody (a nuclear helicase protein) positivity, classical DM can be considered with a favorable course. The positivity of anti Mi-2 identifies a reduced propensity to ILD and a better response to therapy. Skin sign frequently associated to anti Mi-2 positivity are Gottron’s papulae, the V sign, the Shawl sign and cuticular hyperkeratosis.38, 39

CLASSIC DM WITH JO-1 ANTIBODY POSITIVITY (t-Istidil Synthase Syndrome)

The association of anti Jo-1 positivity to DM describes a subset of the disease which often presents ILD and poor response to therapy. Beside, the t-istidil synthase syndrome is accompanied by myositis, non-erosive arthritis less frequently and by constitutional symptoms, skin rash or sicca syndrome. Main skin lesions are mechanic’s hands and Raynaud phenomenon.39, 40

AMYOPATIC DM

Amyopathic DM (ADM) is a DM characterized by the absence of muscle involvement and muscle enzyme elevation for at least of six months. ADM has a lower correlation with neoplasm compared to classical DM. Typical skin lesion in ADM are Gottron’s papulae, heliotrope rash, nail abnormalities and poikiloderma.41

PARANEOPLASTIC DM

Different clinico-laboratoristic characteristics have been associated to paraneoplastic DM (PDM) to favor an early diagnosis.52 Among the different PDM characteristics that suggest the presence of a neoplasm there are: necrotic lesions, vasculitides, pruritus, erythroderma (more than 90% of body surface area involved) end the presence of Gottron’s papulae.43, 44

IATROGENIC DM

Iatrogenic DM is usually induced by different types of drugs which some induce skin and muscle symptoms (chloroquine, cimetidine clofibrate,
Therapy

Treatment of DM skin lesions is difficult. Therapies need to be individualized, also, on the base of muscle and systemic involvement. While muscle symptoms usually respond to systemic corticosteroid, skin lesions may persist. In some cases, skin lesions recede during the treatment of the underlying pathology (e.g. cancer); if it’s not the case, a specific therapy should be suggested.

Both UV-A and UV-B light may trigger or worsen skin lesions; thus the avoidance of sun exposure, the diligent use of sunscreens (SPF≥50) as well as the use of sun protective clothing and wide-brimmed...
CUTANEOUS SIGNS OF CLASSICAL DERMATOMYOSITIS

A URIEMMA

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Mycophenolate mofetil (MMF) has been shown to be an alternative steroid-sparing agent at the dosage of 1000 mg twice daily, in course of DM, for both systemic and cutaneous involvement. Azathioprine (AZA) is a steroid-sparing agent widely used in dermatologic conditions. However the lack of data on AZA in DM skins disease seems not to suggest its use for cutaneous DM.

Topical corticosteroid drugs (class I and II) twice-daily may be recommended when pruritus and burning sensation are present. The usage of occlusive dressing usually enhances the therapeutical efficacy. To avoid side effects, in case of prolonged use, a cyclic therapy is recommended.

Also topical calcineurin inhibitors (CNIs) such as tacrolimus and pimecrolimus can be used for the treatment of cutaneous DM signs in a twice-daily bases, for 6-8 weeks. These agents have been proved to be safe and effective in combination with systemic therapies rather than alone, or for long term therapies in atrophogenic areas.

In more refractory cases of skin DM lesions systemic antimalarials have been used. Their mode of action is still under investigation; however they exert immunomodulatory, antinflammatory and anti proliferative effect together with sun protective activities. Hydroxychloroquine sulfate in best used at a dose of 200-400 mg/day while chloroquine phosphate in a dose of 250-500 mg/day. Antimalarians can be used as sole therapy or in combination with other systemic or topical therapies.

Although systemic corticosteroids are the first option in case of myositis, the discordant response to therapy between muscle and cutaneous manifestations and their adverse effects, limit their use to concomitant or alternative therapy for skin DM lesion. Usually prednisone is used at a dosage of 1 mg/kg/day tapered over 2-3 months for particularly symptomatic skin DM lesions. In the course of JDM, corticosteroid can be of interest in preventing or rapidly reducing lesions like calcinosis cutis.

Methotrexate (MTX) is a useful therapy in patients with more resistant cutaneous DM and may control DM-associated myositis. For that reason MTX can be considered as first line steroid sparing agent. The efficacy of MTX has also been reported in cutaneous disease in JDM. The typical starting dose is 10 mg/week orally or subcutaneously with folic acid supplementation 1 mg daily.

Management of pruritus and burning sensation is a special aspect of DM treatment. In moderate cases associated with xerosis, emollients and moisturizing creams are often useful. In more severe cases, oral sedating antihistamines, such as hydroxyzine 10-50 mg or non-sedating antihistamines in day-time or Doxepin and amitriptyline (long-acting tricyclic antidepressants with potent antihistaminic effects) as well as gabapentin and pregabalin can be used.

Conclusions

Although DM represents the most common subtype of IIM is actually a great masquerade. Skin signs are the hallmark of the disease and usually lead the correct diagnosis. DM related skin signs could be classified as pathognomonic, highly characteristics and compatible.

Skin signs usually precede the onset of general symptoms or can represent the only manifestation of DM (amiopathic DM). Actually DM has to be addressed as a probable paraneoplastic syndrome and those skin signs are important not only for diagnosis, being sometimes correlated with diseases course. However treatment of cutaneous signs of DM is sometimes difficult ad a combination of topical and
system agents is necessary. Some other, the avoidance of sun exposure and the use of a sun filter cream is enough to reduce skin manifestation.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

An update on juvenile dermatomyositis

V. BOCCALETTI, S. DI NUZZO, C. FELICIANI, G. FABRIZI, C. PAGLIARELLO

Juvenile dermatomyositis (JDM) is a rare, severe, autoimmune disease characterized by a small-vessel vasculopathy that primarily affects skin and muscle, but also lung, joints, gut and heart. Nowadays prompt recognition of this entity and aggressive treatment, when needed, improves outcomes and has decreased mortality that, before corticosteroid became a mainstay in therapy, could reach 40%.

Key words: Dermatomyositis - Autoimmune diseases - Vascular diseases.

Incidence of juvenile dermatomyositis (JDM) varies between 2 and 4 children per million per year with some minor variations between ethnic groups and is more frequent in females with a male:female ratio of 1:2.3, even if it could be lower in younger age groups. Median age of onset is around 7 years, although 1 case out of 4 starts before 4 years of age, indicating a worst prognosis.

Typical rashes in JDM include a generalized photosensitive erythema, periorbital heliotrope rash (Figures 1, 2) and Gottron’s papules over the extensor surfaces (Figure 3), that are diagnostic and pathognomonic. Proximal muscle weakness may precede, follow or be present at the same time of the cutaneous rash and is fundamental for the diagnosis. Actually, in the majority of children, a number of minor systemic signs can be present such as fever, anorexia, malaise, abdominal pain, irritability, weight loss.

A diagnosis of definite JDM, based on classic criteria of Peter and Bohan, consisted of typical skin rash and, at least three of the following: 1) muscle weakness; 2) elevation of muscle enzymes; 3) abnormal EMG suggestive of myopathy; 4) abnormal muscle biopsy sample suggestive of inflammatory myopathy (Table I) even if the Childhood Arthritis and Rheumatology Research Alliance (CARRA) has recently proposed to introduce MRI study of muscles instead of biopsy as an acceptable tool to assess myositis and its good correlation with disease activity (Table II).

Pathogenesis

While the pathogenesis of JDM still remains unclear, the most recent hypothesis is that the interactions between environmental factors (infections, vaccinations and drugs) and an immune dysfunction in a genetically susceptible patient could generate the disease. Recent studies show that the ancestral haplotypes HLA-B*08, DRB1*0301 and DQA1*0501 may confer extended risk to develop myositis in Caucasian children and adults, and also JDM.

The clinical manifestations of JDM are mainly due to a small-vessel angiopathy in which deposition and activation of the complement cascade determines a perivascular inflammation and endothelial dysfunction and finally in a depletion of capillaries. Consequently, this will determine tissue damage (in
skin, in muscles) with dilated capillaries and fiber atrophy. There is mounting evidence of a strong role for type I Interferons in both adult and JDM, for which a major source are activated plasmacytoid dendritic cells. These cells in the skin could be activated by toll-like receptors after various stimuli (viral infections, UV, tissue damage) while the resident

Table 1.—Bohan and Peter criteria (1975).

| Major: typical cutaneous rash |
| Minor: proximal muscle weakness |
| – ↑ CPK, ↑ LDH, ↑ transaminasis, ↑ aldolasis |
| – abnormal EMG and histology suggestive for dermatomyositis |

Diagnosis: 1 major criteria + 3 minor criteria
Uncertain diagnosis if: 1 major criteria + 2 minor criteria

Figure 1.—Periorbital erythema without edema.
Figure 2.—Typical picture of dermatomyositis on the hands.
Figure 3.—Gottron’s papules.
ones in muscle may be activated after endothelial damage and vasculopathy. Plasmocytoid dendritic cells also secrete chemokines which may contribute to the formation of lymphocyte aggregates, typically perivascular.11 Auto-antibodies may contribute to the formation of immune complexes that are chemotactants for other inflammatory cells and enhance inflammation with overexpression of type I interferons.13

**TABLE II.**—*Diagnostic criteria.*

Typical cutaneous manifestations + 3 signs:

a. muscle weakness  

b. ↑ muscle enzymes  

c. abnormal EMG  

d. muscle histology suggestive for dermatomyositis  

e. myositis signs using magnetic resonance

Modified by CARRA 2006 (Childhood Arthritis and Rheumatology Research Alliance).

**TABLE III.**—*Antibodies myositis-specific (MSAs) and Antibodies myositis-associated (MAAs)*

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Antigen</th>
<th>Clinical picture associated to JDM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-ARS</td>
<td>Aminoacyl-tRNA synthetase</td>
<td>Weakness, arthritis, Raynaud, fever, interstitial lung fibrosis</td>
</tr>
<tr>
<td>Anti-JO-1</td>
<td>Histidyl-tRNA synthetase</td>
<td></td>
</tr>
<tr>
<td>Anti-PL-12</td>
<td>Alanyl-tRNA synthetase</td>
<td></td>
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<tr>
<td>Anti-PL-7</td>
<td>Threonyl-tRNA synthetase</td>
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</tr>
<tr>
<td>Anti-EJ</td>
<td>Glicyl-tRNA synthetase</td>
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<tr>
<td>Anti-OJ</td>
<td>Isoleucyl-tRNA synthetase</td>
<td></td>
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<tr>
<td>Anti-KS</td>
<td>Asparaginyl-tRNA synthetase</td>
<td></td>
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<tr>
<td>Anti-Ha</td>
<td>Tyrosyl-tRNA synthetase</td>
<td></td>
</tr>
<tr>
<td>Anti-Zo</td>
<td>Phenylalanyl-tRNA synthetase</td>
<td></td>
</tr>
<tr>
<td><strong>Other MSAs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Anti-MI-2</td>
<td>DNA helicase</td>
<td>JDM with severe and recalcitant polymyositis</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>Signal Recognizing Proteins</td>
<td></td>
</tr>
<tr>
<td><strong>New autoantibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-p155/140 o</td>
<td>γ subunit of transcriptiona intermediate factor (TIF)-1-γ</td>
<td>Severe cutaneous manifestations, generalized lipodystrophia</td>
</tr>
<tr>
<td>Anti-p155</td>
<td>MJ autoantigen (??), Nuclear matrix protein NXP2</td>
<td>Calcinoisis</td>
</tr>
<tr>
<td><strong>MAA-s</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-U1-RNP</td>
<td>Ribonucleoprotein U1 (snRNP)</td>
<td>Overlap with scleroderma</td>
</tr>
<tr>
<td>Anti-U3-RNP</td>
<td>Ribonucleoprotein U3 (fibrillarin)</td>
<td>Overlap with scleroderma</td>
</tr>
<tr>
<td>Anti-PM-Scl</td>
<td>Ribonucleoprotein 52 o 60 kD (hYRNA)</td>
<td>Overlap with scleroderma</td>
</tr>
<tr>
<td>Anti-Ro</td>
<td>Eterodimer p70/p80, DNA associated protein</td>
<td></td>
</tr>
<tr>
<td>Anti-La</td>
<td>DNA topoisomerase I</td>
<td></td>
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<tr>
<td>Anti-Ku</td>
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<tr>
<td>Anti-Topo</td>
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**IMACS**  
Medical evaluation  
Patient / parents evaluation  
Muscle condition  
Functional condition  
Laboratory tests  
Overall activity  
Non-muscle activity  
Quality of life

**PRINTO**  
Global medical assessment using VAS or Likert scale  
Patient / parents assessment using VAS or Likert scale  
MMT, CMAS  
CHAQ  
Not included  
Not included  
CHQ global physical score

PRINTO, Paediatric Rheumatology International Trials Organisation; IMACS, International Myositis Assessment and Clinical Studies Group; IIM, Idiopathic inflammatory myopathy; JDM, Juvenile dermatomyositis; VAS, Visual analogical scale; MMT, Manual Muscle test; CMAS, Childhood Myositis Assessment Scale; CHAQ, Childhood Health Assessment Questionnaire; CK, creatine kinase; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAS, Disease Activity Score; MDAAT, Myositis Disease Activity Assessment Tool, including MYOACT (Myositis extra-skeletal muscle disease activity assessment by VAS) and MITAX (Myositis intention to treat activity index); QOL, quality of life; CHQ, Childhood Health Questionnaire.
Autoantibodies are common in JDM and classically can be divided into two categories: myositis-specific Ab (MSA) directed at nuclear or cytoplasmic components that are involved in protein synthesis (aminoacyl-tRNA synthetase) or nuclear transcription and myositis-associated Ab (MAA), which are found in other autoimmune conditions and overlap syndromes (Table III). Around 70% of children affected by JDM are positive to some MSA or MAA with similar clinical characteristics to adults, according to the positive autoantibody: e.g., lung involvement is more frequent in anti-Jo-1 positive patients while anti-Mi-2 patients run a less severe course. Analysis of the same data tells us that about 30% of the same cohort of patients with JDM and ANA-positivity are ENA-negative, pointing out the fact that research of new autoantibodies is still needed to better define more patients subgroups. Recently antip155/140 was described that confers a higher risk to develop lypodistrophy and a more severe cutaneous involvement, and others are under study.

**Long-term outcome**

Based on clinical course, DMG patients are divided in three different groups:

1. monocyclical, patients who present complete remission within two years;
2. polycyclical, patients who shows several episodes of recurrence of disease;
3. patients with continuous chronic disease.

Due to recurrence or continuous symptomatic disease, patients included in the second and third group present a more severe cumulative skin damage compared to the first one. However, severe course leading to death, nowadays, is a rare event (1% to 3% of the patient population) and occurs as consequence of severe infection in patients with heavy immunosuppressive treatment. On the other hand, overall morbidity of disease is not negligible. Anecdotal report on the occurrence of malignancies in DMG patients does not suggest a routine follow-up, which must be considered in case of specific symptoms and signs of disease, such as splenomegaly. During infancy, skin ulcers, soft tissue damage and calcynosis due to vascular flogosis are reported. Studies on the long-term outcome showed that after eight years of continuous disease, 10% and 40% of patients had severe and moderate muscular weakness, respectively. In these patients involvement of any organ occurs in almost 70% of them: skin (calcynosis 23%, which is more frequent than adults; lypoatrophy around 10%) and muscles more frequently; bone (ankilosis, and osteoporosis), endocrine glands (delayed growth and hirsutism), gastrointestinal tract (dysphagia). In literature, involvement of respiratory tract in children is scarcely reported, sometimes an asymptomatic reduction of respiratory function occur. Female are more prone to severe prognosis.

**JDM treatment**

A definitive treatment strategy for JDM patients remain elusive because of lacking of clear, evidence based prognostic factors. Many studies have shown that deferring treatment onset as well as a low dose treatment are linked to worse outcomes and could also promoting calcinosis development.

Systemic corticosteroids are the mainstay of JDM, at least at its onset. A standard therapeutical approach is represented by prednisone 1-2 mg/kg/day for at least four weeks, tapering by 20% each two weeks if a favorable response is achieved. When the dosage of 0.5 mg/kg/day is reached, treatment could be reduced by about 20% per fortnight till its complete discontinuation.

Other authors suggest to induce a clinical remission through high dose intravenous methylprednisolone bolus therapy at dosage of 5-30 mg/kg/day for three days and then using the aforementioned oral prednisone treatment. If a complete remission could not be achieved with this regimen, it was suggested to introduce steroid sparing agents such as methotrexate (MTX) or cyclosporine (Cya). When choosing to use MTX, the dose should be increased in order to reach the full dosage of 15 mg/m² and then maintained for at least two years. Intravenous immunoglobulin (IVIG) administration could not be routinely recommended because of limited evidence of its effectiveness and its high cost.

Biologic drugs for JDM treatment have also limited evidence of effectiveness. Some case series have suggested that infliximab could be useful for the management of refractory cases of JDM at the dosage of 6 mg/kg per week, administered at week 0, 2 and 6 and then every 4-6 weeks. Nevertheless, JDM seems a IFN-1 driven pathology and there is
conflicting evidence about the role of TNF-α in its pathogenesis.\textsuperscript{31}

A promising drug is rituximab, which acts through selective CD20 positive B lymphocytes depletion. Recently, a study involving 200 refractory myositis including 48 adult and childhood DM have shown a relevant effectiveness after 44 weeks of treatment, although adverse events were acknowledged as a potential issue.\textsuperscript{32}

Finally, another study by Levy \textit{et al.}\textsuperscript{33} suggests that for early diagnosed JDM (symptoms onset from less than 8 weeks) IVIG monotherapy without systemic steroids administration represents a safe and effective alternative devoid of severe side effects.

Conclusions

JDM should be regarded as a systemic disease affecting mainly skin and muscles as principal targets. The course of JDM could also progress to a severe form, therefore, its early diagnosis is of paramount importance. JDM diagnosis could be supported by imaging techniques such as MRN, that for selected cases in appropriate clinical setting could replace the EMG and even muscle biopsy. Clinical course of the disease and treatment response should be evaluated by validated and disease specific clinical scores. Besides of systemic corticosteroids, new biologic drugs (such as monoclonal antibody against the protein CD20) and IVIG seems promising and deserves consideration for recalcitrant cases. Future studies should better assess the role of these new and expensive treatments as steroid sparing agents in the routine clinical practice.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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The association between idiopathic inflammatory myopathy (IIM) and cancer has been extensively studied in adults. Many epidemiological studies demonstrated this association, which appears stronger for dermatomyositis (DM) than for polymyositis (PM). The first case suggesting an association between cancer and DM was reported in 1916. At present the reported incidence of cancer association with DM varies widely, from less than 7% to over 30%. Many early evidences came from case reports, but this association was later confirmed in case-control as well as in population-based studies. Ovarian cancer or breast cancer in females and lung cancer in males are the main malignancies associated with DM. Given the frequency of the association of dermatomyositis with cancer, for cost-effectiveness reasons it might be important to develop simple and appropriate diagnostic tests for identification of patients with DM, who may be at higher risk of developing a malignancy. Clinicians should plan follow-up schedules to optimize both cancer detection and treatment, and thus to improve patient survival. Many different clinical and serological signs have been suggested as possible predictive factors for malignancy in dermatomyositis: age, increased erythrocyte sedimentation rate (ESR), presence of cutaneous leukocytoclastic vasculitis, cutaneous rash and skin lesions as cutaneous necrosis and periungual erythemas, neoplastic markers or dysphagia. The results of the different studies are quite discordant. Therefore, we conducted a systematic review of the scientific literature to evaluate the level of the risk of cancer in patients with dermatomyositis and to explore whether certain patient characteristics may be linked to different levels of cancer risk.

Key words: Dermatomyositis - Neoplasms - Skin diseases.

Dermatomyositis (DM) is an autoimmune disease characterized by a symmetric proximal, extensive, inflammatory myopathy and a characteristic cutaneous eruptions. Several subtypes of DM have been described such as: classical, juvenile, overlap, amipathic, drug induced and cancer associated. The association between idiopathic inflammatory myopathy (IIM) and cancer is well demonstrated in adults and several epidemiological studies have confirmed this association, as well as that cancer risk is greatest in patients with DM. The reported incidence of cancer varies widely in the published literature from less than 7% to over 30%.1,2

The first reports suggesting this association were published in 1916, when Sterz and Kankeleit described the first case of DM and gastric cancer. Early studies were limited by the absence of diagnostic criteria for DM. The criteria established in 1975 by Bohan and Peter for diagnosis of dermatomyositis are presently considered the “gold standard” in clinical studies and in trials, although the authors themselves stated that failure to fulfill these criteria cannot completely exclude a diagnosis of dermatomyositis or polymyositis (PM). The frequency of cancer in myositis detected by Bohan and Peter was 8.5%, with a
higher risk of malignancy in patients with dermatomyositis.\textsuperscript{3}

The heterogeneity of the data reported in the literature depends on the heterogeneity of the samples (e.g., from the ethnicity of the study population, the different criteria for the diagnosis of DM/PM, the inclusion of patients with tumors temporally unrelated to DM, the diverse duration of the follow-up periods) and the lack of appropriate control groups.

Sigurgeisson \textit{et al.},\textsuperscript{4} estimated the percentage of cases of malignancy in the course of myositis, analyzing within a population-based study in Sweden, a sample of 788 DM/PM patients, utilizing data from a national register. He found 392 patients with DM, 61 of whom had a malignancy, and 59 of these were diagnosed at the same time or shortly after the diagnosis of DM. Airio \textit{et al.},\textsuperscript{5} in 1995, revised a national registry of diseases in Finland, which covered a period between 1969 and 1985, and described 175 cases of PM and 71 patients with DM, finding 34 cases of malignancy associated with myositis (30 with DM and 4 with PM). Patients at higher risk were those with DM and aged more than 50 years, and in whom the diagnosis of DM was made within one year.

Stockton \textit{et al.}\textsuperscript{6} selected patients with an initial diagnosis of DM or PM from the Scottish hospital registry between 1982 and 1996 and identified malignancies in their cohort through a cross search in the National Cancer Registry. They concluded that there was an overall increased risk of malignancy for DM with a standardized incidence ratio (SIR) of 7.7 (95% confidence interval [CI]=5.7 to 10.1).

Buchbinder \textit{et al.}\textsuperscript{7} identified all patients with biopsy-proven IIM diagnosed in the state of Victoria, Australia, from 1981 to 1995 from the Victorian Neuropathology Service, which has reviewed all muscle biopsies performed in that state since 1981. The State Cancer Registry and National Death Registry were used to identify malignant disease to the end of 1997 or death, if earlier. Also these authors observed an increased risk for malignant disease in DM (SIR=6.2; 95% CI=3.9-10.0). This risk remained elevated even when the first year of follow-up after diagnosis of myositis was excluded from the statistical analysis (SIR=4.3; 95% CI=2.3-8.1).

Many other case-control and cohort studies are reported in the scientific literature. However, even though they all include an appropriate control group, and adopt a more strict disease definition, these studies have reached conflicting conclusions regarding the association between myositis and cancer.

Two meta-analyses examine the results of epidemiological studies. The first is from Zantos \textit{et al.},\textsuperscript{8} who in 1994 reviewed 4 case-control or cohort studies. Taken together, these reports provided 565 cases of PM and 513 cases of DM for a total of 1078 myositis cases. There were 97 cancers diagnosed in the DM group and 56 cancers in the PM group over a period of 10 years, from 5 years prior the diagnosis of myositis through 5 years after it. The pooled odds ratios (OR) for the association with cancer were 4.4 for DM (95% CI, 3.0-6.6) and 2.1 for PM (95% CI 1.4,3.3). Since the risk of cancer in DM was high both before and after the diagnosis of DM, the authors concluded that the DM may be regarded as a paraneoplastic phenomenon.

The second pooled analysis was performed by Hill \textit{et al.}\textsuperscript{9} They analyzed the published national data from Sweden, Denmark and Finland concerning DM and cancer. They found 618 cases of DM of whom 198 had cancer, 115 of these had developed after the diagnosis of DM.

Several features have been reported as possible prognostic indicators for cancer development.\textsuperscript{10,11} Anyway, most of the previous studies were small in size and failed to draw sound conclusions. Wang \textit{et al.}\textsuperscript{12} published in 2013 a meta-analysis of 20 previously published observational studies and suggested that age, gender, cutaneous necrosis, dysphagia, arthritis and lung complication may influence to cancer development in DM/PM patients.

In order to confirm these data and to possibly identify other clinical and laboratory characteristics associated with malignancy in DM, we performed a deeper literature search including more case-series studies. We report here the results concerning the information about signs and symptoms that may be associated with a higher risk of cancer in DM.

\textbf{Methods}

Our systematic review of the English literature covered the period from 1969 through March 2011. According to the criteria described in detail here below, we identified all the original studies (i.e., whether retrospective, prospective, case-control, cohort studies, and case series) evaluating the association of DM with and malignancies. We also included previous reviews as well as letters to the editor.
Information source and search strategy

The search for relevant articles was conducted on the following electronic database: Pubmed/Medline, Ovid and Embase. Search terms included: dermatomyositis and malignancy, dermatomyositis and cancer, dermatomyositis and tumor, dermatomyositis and neoplasm. Articles published before 1969 were excluded because of lack of detailed data and of the difficulty in assessing the validity of the diagnoses, due to the lack of established diagnostic criteria at that time.

From these simpler search terms a combined strategy was developed, as shown in Figure 1.

The four “single search terms” yielded preliminary lists including 1260, 1243, 1297 and 1171 articles, respectively yielding a total of 4971 potentially relevant articles. Subsequently, duplicate articles were excluded and after this phase the number of selected items was reduced to 1207 titles. In a further phase, articles in non-English languages, case reports, and studies that included patients affected by amyopathic dermatomyositis, polymyositis, juvenile myositis, inclusion body myositis, and tissue connective diseases (CTD) and overlap syndrome were also excluded.

Two reviewers, independently screened these articles for inclusion. Articles were read in full text if at least one of the two reviewers considered an abstract to be potentially relevant. This phase of the screening process identified 208 items, which underwent a full text appraisal. Of these, only the studies that fulfilled the following prespecified eligibility and ineligibility criteria were chosen for the analysis.

Eligibility criteria were: case series of at least ten patients affected by classic dermatomyositis and in whom the association with cancer was studied; articles in English language; articles published after 1969.

Ineligibility criteria were: case reports and case series with fewer than ten classic DM patients; studies of patients with amyopathic DM, polymyositis, juvenile myositis, inclusion body myositis, myositis and tissue connective diseases (CTD) and overlap syndrome; articles in languages other than English; articles published before 1969.

Conflicts were resolved through discussion.

A flow diagram (Figure 2) illustrates the selection process for the articles included in the review. Exceptionally, 4 studies 25, 41, 43, 77 reporting less than 10 patients affected by classic dermatomyositis were included, because they were considered of particular interest for our review, given the presence of data concerning paraneoplastic DM. A total of 85 articles were assessed for quantitative and qualitative analysis and underwent data extraction.

Data collection process

Data extraction from reports on DM concerned: authors, date of publication, duration of follow-up, study location, data collection period, sample size, number of patients with associated malignancy, sex, weighted mean age. Patients were divided in two study-groups, “paraneoplastic dermatomyositis” and “classic dermatomyositis”, and the following data were also recorded: cutaneous signs such as skin necrosis, Raynaud’s phenomenon, periarticular erythema, heliotrope erythema, Gottron’s papules, Gottron’s sign, periangual erythema and/or nail fold telangiectasia, cutaneous ulceration, poikiloderma, cutaneous vasculitis, and capillaroscopy signs such as megacapillaries. Moreover systemic involvement signs such as dysphagia and/or dyspnea, rapid
onset, fever, interstitial lung disease, arthralgia, resistance to treatment, distal muscle weakness and serological signs such as positivity for different autoantibodies like antinuclear antibodies (ANA), extractable-nuclear antibodies (ENA), myositis-specific antibody (MSA), anti Jo-1 antibodies, anti 155/140 antibodies, anti-RNP antibodies were recorded.

**Data synthesis**

The frequency (%) of malignancy in DM patients was obtained for the different studies, in order to input in the calculation of the pooled estimates. Frequency (%) of cutaneous, systemic and serological signs in both patient study groups were calculated. Relative risk (RR) and 95% confidence interval (CI)
were computed using EpiInfo (version 3.5.1). Classically, the RR is a dimensionless number resulting from the ratio of two risks.

**Results**

Eighty-five reports evaluating the association of dermatomyositis and malignancy were retrieved. Simple size ranged from 6 to 1059 patients. When pooled, these reports provided 8712 cases of dermatomyositis. We found 1784 cases of DM associated with malignancy, yielding a rate of 20.5%. The highest cancer rate in a single study was 10/11, or 90.9%, while a case series reported a rate of 2.5%, or 1/40. The results of the literature review are summarized in Figure 3.

None of the studies reported all the characteristics we wanted to analyze. On the other hand, each selected study showed only few characteristics we

![Figure 3](image-url).—Description of all retrieved records: number of cases (%) of DM associated with malignancy.
were interested in. In order to overcome this issue each time we chose studies within the 85 original papers that recorded the variable to be examined.

Relative risk (RR) of malignancy in DM by gender

Data about gender of patients was available only in 44 out of the 85 studies retrieved. This refinement yielded 6152 DM patients of which 4195 were female and 1957 male. The pooled rate of cancer in male patients was 476/1957, or 24.3%. The highest reported malignancy rate, in three different studies, was 100%. Of the 4195 female patients, 629 were associated to malignancy, with a rate of 15%.

The relative risk of cancer in DM was significantly elevated in the male vs. female patients (RR 1.6; CI 95% 1.44-1.78) (Figure 4).

Figure 4.—Relative risk of cancer in dermatomyositis in male vs. female patients.
Clinical and serological features and risk of malignancy

We selected within the 85 original reports different studies that analyzed the following characteristics: cutaneous necrosis (N=6),16, 20, 26, 32, 40, 70 Raynaud's phenomenon (N=9),13, 21-24, 26, 45, 49, 67 periorbital erythema (N=9),13, 20, 22, 40, 45, 64, 67, 73 heliotrope erythema (N=18),3, 13, 20, 22-26, 29, 40, 41, 43, 45, 59, 64, 65, 67, 73 Gottron's papules (N=13),13, 20, 22, 26, 40, 41, 43, 45, 64, 65, 67, 73 Gottron's sign (N=8),17, 22, 23, 24, 29, 45, 62, 67 periungual erythema and/or nail fold telangiectasias (N=10),13, 16, 17, 20, 23, 24, 40, 45, 62, 65 cutaneous ulceration (N=7),13, 20, 22, 40, 45, 62, 67 poikiloderma (N=6),13, 26, 29, 45, 65, 73 cutaneous vasculitis (N=5),29, 34, 37, 41, 42 capillaroscopy signs such as megacapillaries (N=6),20, 26, 29, 40, 49, 73 dysphagia (N=17),13, 16, 21, 22, 26, 27, 34, 41, 44, 45, 49, 55, 59, 62, 65, 67, 79 dyspnea (N=7),16, 17, 21, 27, 41, 46, 67 rapid onset (N=3),16, 21, 66 fever (N=5),17, 22, 26, 45, 67 interstitial lung disease (N=18),13, 20, 22-25, 34, 44, 45, 49, 57, 62, 67, 68, 72, 81, 85, 86 arthralgia (N=14),3, 13, 16, 17, 22-26, 34, 40, 41, 45, 67 resistance to treatment (N=13),22, 24, 31, 33, 37, 40, 41, 49, 57, 62, 67, 83 distal muscle weakness (N=17)

Table I.—Frequency (%) of clinical cutaneous signs in paraneoplastic DM patients and RR vs. classic DM patients.

<table>
<thead>
<tr>
<th></th>
<th>Classic DM</th>
<th>Paraneoplastic DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total of patients</td>
<td>N. of cases</td>
</tr>
<tr>
<td>Cutaneous necrosis</td>
<td>260</td>
<td>13</td>
</tr>
<tr>
<td>Ulceration</td>
<td>189</td>
<td>20</td>
</tr>
<tr>
<td>Heliotrope erythema</td>
<td>565</td>
<td>391</td>
</tr>
<tr>
<td>Gottron’s papules</td>
<td>446</td>
<td>244</td>
</tr>
<tr>
<td>Periungual erythema</td>
<td>224</td>
<td>98</td>
</tr>
<tr>
<td>Megacapillaries</td>
<td>254</td>
<td>99</td>
</tr>
<tr>
<td>Gottron’s sign</td>
<td>238</td>
<td>134</td>
</tr>
<tr>
<td>Cutaneous vasculitis</td>
<td>283</td>
<td>213</td>
</tr>
<tr>
<td>Poikiloderma</td>
<td>199</td>
<td>113</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>531</td>
<td>117</td>
</tr>
</tbody>
</table>

Table II.—Frequency (%) of clinical systemic signs in paraneoplastic DM patients and RR vs. classic DM patients.

<table>
<thead>
<tr>
<th></th>
<th>Classic DM</th>
<th>Paraneoplastic DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total of patients</td>
<td>N. of cases</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>557</td>
<td>146</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>136</td>
<td>32</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>439</td>
<td>209</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>422</td>
<td>194</td>
</tr>
<tr>
<td>Rapid onset</td>
<td>108</td>
<td>29</td>
</tr>
<tr>
<td>Refractory to therapy</td>
<td>218</td>
<td>110</td>
</tr>
<tr>
<td>Fever</td>
<td>252</td>
<td>82</td>
</tr>
<tr>
<td>Intertitial lung</td>
<td>468</td>
<td>140</td>
</tr>
</tbody>
</table>

17, 22-24, 29, 40, 41, 43, 45, 47, 57, 62, 64, 65, 67, 73, 74, 77 and positivity for different auto-antibodies like antinuclear antibodies (ANA) (N=18),13, 16, 20-22, 24-26, 29, 34, 40, 41, 45, 47, 53, 59, 67, 68 extractable-nuclear antibodies (ENA) (N=9),22, 26, 29, 40, 42, 59, 67, 68, 81 myositis-specific antibody (MSA) (N=2),68, 84 anti Jo-1 antibodies (N=10),13, 22, 24, 26, 29, 57, 67, 68, 84, 85 anti 155/140 antibodies (N=5) 84-87, 90 and anti RNP antibodies (N=3).34, 84, 85

The pooled results from the literature review, concerning the rates of clinical and serological signs in DM patients with and without malignancy are summarized in Tables I-III.

Paraneoplastic DM was more frequently associated with cutaneous necrosis, compared to Classic DM patients (34% vs. 5%; RR 6.1; P<0.001). In addition, DM presenting with dysphagia, muscle weakness, arthralgia and anti-155/140-Ab positivity was associated with a higher risk of cancer. The RR for dysphagia, arthralgia, and anti -155/40 Ab positivity was of 1.8 (95% CI 1.5-2.2; P<0.001), 1.3 (95% CI 1.2-1.5; P<0.001), and 5.4 (95% CI 3.7-8.1; P<0.001), respectively, for paraneoplastic DM patients vs. classic DM.
Table III.—Frequency (%) of antibodies positivity in paraneoplastic DM and RR vs. classic DM patients.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Total of patients</th>
<th>N. of cases</th>
<th>%</th>
<th>Total of patients</th>
<th>N. of cases</th>
<th>%</th>
<th>RR</th>
<th>95% CI</th>
<th>P&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti 155/140 Ab</td>
<td>237</td>
<td>29</td>
<td>12.2%</td>
<td>48</td>
<td>32</td>
<td>66.7%</td>
<td>5.4</td>
<td>3.7-8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti RNP Ab</td>
<td>129</td>
<td>9</td>
<td>7%</td>
<td>36</td>
<td>4</td>
<td>11.1%</td>
<td>1.6</td>
<td>0.5-4.9</td>
<td>0.416</td>
</tr>
<tr>
<td>ANA</td>
<td>714</td>
<td>318</td>
<td>44.5%</td>
<td>260</td>
<td>119</td>
<td>45.8%</td>
<td>1.02</td>
<td>0.9-1.2</td>
<td>0.732</td>
</tr>
<tr>
<td>Anti MSA* Ab</td>
<td>138</td>
<td>65</td>
<td>47.1%</td>
<td>6</td>
<td>0</td>
<td>0%</td>
<td>0.3</td>
<td>0.05-1.9</td>
<td>0.088</td>
</tr>
<tr>
<td>ENA</td>
<td>294</td>
<td>72</td>
<td>24.5%</td>
<td>106</td>
<td>3</td>
<td>2.8%</td>
<td>0.12</td>
<td>0.04-0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti Jo-1 Ab</td>
<td>390</td>
<td>62</td>
<td>15.9%</td>
<td>134</td>
<td>2</td>
<td>1.5%</td>
<td>0.09</td>
<td>0.02-0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Interestingly, instead, Raynaud’s phenomenon (10.3% vs. 22%; RR 0.5; P<0.001), fever (12% vs. 32.5%; RR 0.4; P<0.001), interstitial lung disease (12.5% vs. 29.9%; RR 0.4; P<0.001), and anti Jo-1 Ab positivity (1.5% vs. 15.9%; RR 0.09; P<0.001) were inversely correlated with cancer presence.

Discussion

DM is a rare inflammatory myopathy which has been associated with an increased risk of cancer development. The association of DM with malignancy was first reported in 1916 but only confirmed with recent large, population-based, retrospective cohort studies. The risk of malignancy is highest at the time of or within 1 year of myositis diagnosis. Cancer of the ovary, lung, and gastrointestinal tract are most often associated with DM, particularly in Western nations, while nasopharyngeal carcinoma is commonly associated in Southeast Asia, Southern China, and Northern Africa.

Several studies suggested that specific features of DM occur in association with internal malignancy and may be used to identify patients who may benefit from an extensive evaluation for malignancy. Most authors recommended a cancer screening specific for patient’s age, gender and ethnic background. So colon cancer may be over-represented in patients with DM aged 65 years or more, while ovarian carcinoma may be easier to detect in women with DM.

These recommendations were based on population-based cohort studies examining cancer risk in white populations. In Southeast Asia the risk of nasopharyngeal carcinoma is clearly increased, and thus a cancer type-specific screening according to the different population may be required.

Paraneoplastic DM presents also relevant features when considering age and gender of patients. In the Finnish and Danish population-based cohort studies, an increased risk of malignancy was evident in patients older than 45 to 50 years of age at the time of myositis diagnosis. In the Scottish population-based study there was a increased risk of malignancy for DM patients 45 to 74 years of age. While gender was never considered a consistent risk factor for malignancy. However, in several studies, as in three of four European studies, in one American study and in one Asian study there were higher standardized incidence ratios for men. The recently, published meta-analysis by Wang et al. on the association of DM and Polymyositis with cancer included twenty studies with 380 patients and 1575 controls. The factors that may increase the risk of cancer were older age (WMD 11.41, 95% CI 9.84-12.98), male sex (OR 1.92, 95% CI 1.49-2.48), cutaneous necrosis (OR 5.52, 95% CI 3.49-8.74) and dysphagia (OR 2.41, 95% CI 1.50-3.86). Their results showed that the factors that may provide protection against cancer were arthritis (OR 0.38, 95% CI 0.24-0.61) and ILD (OR 0.32, 95% CI 0.20-0.51).

In our review we were able to retrieve 1784 cases of paraneoplastic DM and 6928 controls, and our estimated rate of paraneoplastic DM was 20.5% in the overall sample. These data are similar to the most precise reports from the population studies which estimated that the cases of paraneoplastic DM are approximately 25% of the total DM cases.
Throughout the literature several prognostic or predictive markers or clinical signs have been proposed to assess the presence of paraneoplastic DM: age, 5.6, 12-14, 29, 32, 38 ESR, 21, 32, 63 cutaneous rash and skin lesion, as cutaneous necrosis, 12, 16, 20, 21, 32, 40, 70, 76 periungual erythemas 13, 20, 32, 76 and ulceration, 13, 22, 45, 67 neoplastic markers, 67, 72 and dysphagia, 12, 13, 27, 32.

However, most studies were able to demonstrate the significance of only one of these factors, or were not coherent with other studies and failed to demonstrate the relevance of one or more of the proposed factors as a predictive feature of malignancy in DM. For example in our previous work, only ESR, out of many proposed clinical and laboratory features, was found to be statistically associated with the presence of malignancy in DM patients. 63

Also the assessment of classical tumor markers is debated. Amoura et al. 72 proposed the diagnostic value of several circulating tumor markers for the detection of solid cancers in DM. They found that cancer antigen (CA) 125 and CA 19-9 were useful in detecting cancer in patients with DM without interstitial lung disease (ILD). However, other authors have not supported this finding. 43

Interstitial lung disease (ILD), 12, 13, 17, 22, 67, 68 arthritis, 12, 13, 22, 25, 67 Raynaud’s phenomenon, 12, 21, 22, 26, 45, 67 fever 22, 67 and high titer of antinuclear antibodies 13, 22, 67 were all proposed as features of reduced risk of a coexisting malignancy. In our study we were able to retrieve and pool a vast set of clinical and serological features, forming a large set of reports. Our results showed that thirteen characteristics were likely to be associated (positively or negatively) with a risk of neoplasm in DM.

Seven characteristics were associated with an increased risk: cutaneous necrosis, heliotrope erythema, dysphagia, dyspnea, muscle weakness, arthralgia and positive anti-155/140 antibodies. On the other hand, six factors were consistently estimated to have a relative risk lower than 1, thus indicating that they may provide some degree of protection against developing a malignancy. These putative protective factors were: Raynaud’s phenomenon, interstitial lung disease, refractory to therapy, fever positive anti Jo-1 antibody and positive ENA antibodies.

Paraneoplastic DM had higher rates of cutaneous necrosis compared with classic DM patients (i.e., 34% vs. 5%; RR 6.1; P<0.001), which is in agreement with the findings from several previous reports. In addition, cases of DM with dysphagia, muscle weakness, arthralgia, and anti-155/140-Ab positivity had an increased risk of cancer with a RR of dysphagia, arthralgia, and anti-155/40 Ab positivity of 1.8 (95% CI 1.5-2.2; P<0.001), 1.3 (95% CI 1.2-1.5; P<0.001) and 5.4 (95% CI 3.7-8.1; P<0.001), respectively for paraneoplastic DM patients vs. patients with classic DM.

In addition, we confirmed the results of some previous reports, when we observed that paraneoplastic DM patients, compared to Classic DM patients, had lower rates of Raynaud’s phenomenon (10.3% vs. 22%; RR 0.5; P<0.001), fever (12% vs.32.5%; RR 0.4; P<0.001), interstitial lung disease (12.5% vs. 29.9%; RR 0.4; P<0.001), and anti Jo-1 Ab positivity (1.5% vs. 15.9%; RR 0.09; P<0.001).

A study by Feldman et al. 41 suggested the presence of a possible association of cutaneous vasculitis with tumor in DM patients, and Hunger et al., 42 in a retrospective study of 23 patients with DM, found that 4 of the 5 cases with an associated malignancy had a histologically-confirmed vasculitis in lesional skin, and their statistical analysis showed that this association was significant (P<0.05), indicating that vasculitis in lesional skin biopsies has a predictive value for the presence of underlying malignancy. In contrast with these findings, our analysis showed no statistically significant difference (P=0.695) for cutaneous vasculitis between two patient study groups, thus suggesting that vasculitis may not be taken into consideration as a malignancy predictive sign.

Recently, several studies examined the role of autoantibodies as potential predictive factors of cancer risk in patients with idiopathic inflammatory myopathies (IIM). 10, 83, 85, 89, 93-96

A new hypothesis proposed that in cancer associated myositis, an immune reaction to the tumor may cross-react with antigens in the skin and muscle, leading to DM. 94, 95

Myositis autoantigens, Mi-2 and Jo-1 were expressed at high levels in myositis muscle, particularly in regenerating muscle fibers, as well as in adenocarcinomas of the lung and breast, but not in the corresponding healthy tissue, demonstrating that tumor cells and undifferentiated myoblasts were antigenically similar. 87

Myositis-specific and myositis associated autoantibodies (MSA, MAA) were present in about 40% of patients with myositis, and they played specific immunopathogenic roles in myositis. MAA include
anti-PM-Scl, anti-Ku, anti-components of the U1 small nuclear RNP (snRNP) or the cytoplasmic Ro antibodies such as Ro60/SSA, La/SSB, and Ro52.93

Among MSAs anti-synthetases were frequently used in screening test and of these the anti-histidyl tRNA synthetase (Jo-1) antibody was the most common. In patients with myositis the anti-Jo-1 antibodies were frequently associated with ILD, Raynaud’s phenomenon, arthopathy and “mechanic’s hands”. A negative association had been noted with this antibody and paraneoplastic DM.85, 93 More recently, a new antibody has recently been reported in DM patients with malignancy in the absence of ANA. Targoff et al.90 first described anti 155/140 antibody in six of eight adult patients with myositis and malignancy. In a further small study, Kaji et al.86 described anti 155/140 antibody in five of seven adult patients with paraneoplastic myositis. In both studies, none of the anti-155/140 antibody-positive patients had ILD, confirming the proposed negative association between ILD and cancer. Trallero-Araguas et al.90 recently confirmed that anti 155/140 auto-antibody may be strictly linked with cancer in patients with DM. Their analysis included 312 adult patients with DM pooled from six studies. The sensitivity and specificity of anti-155/140 for diagnosing cancer-associated DM were 78% (95% CI 45-94%) and 89% (95% CI 82-93%), respectively. Anti 155/140

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*Figure 5.—Proposed strategy for the identification of DM patients at increased risk of malignancy.*
had positive and negative predictive values of 58% and 95%, respectively. In a study by Chinoy et al., the anti 155/140 antibody was DM-specific and had 50% sensitivity and 96% specificity for cancer-associated myositis. When combined with negative results of hospital-based routine testing for Jo-1, Ku, PM-Scl, U1-RNP antibodies, a positive anti 155/140 antibody result had 94% sensitivity and 99% negative predictive value.

Our pooled analysis confirmed these data of the literature, since we observed that patients with a positive anti-155/140 antibody test have a 5.4 RR of having cancer compared to anti-155/140 antibody negative patients (95% CI 3.7-8.1; P<0.001).

Other statistically significant results we obtained concerned the positivity of ENA and anti-Jo-1 antibodies. The presence of these antibodies is negatively associated with cancer, indicating a possible protective effect, with a RR of 0.12 (95% CI 0.04-0.4; P<0.001) and 0.09 (95% CI 0.02-0.4; P<0.001), respectively in paraneoplastic DM compared to the non-malignant variant. Our analysis did not show an association between ANA auto-antibodies and cancer development.

Unfortunately, we were not in a position to examine others relevant laboratory tests (e.g., ESR, aldolase, creatine chinas, lactate dehydrogenase) because of the excessive heterogeneity in the type of reported factors in the different studies.

In accordance with data already reported in the literature, a proposed strategy for the identification of patients with DM, who may be at increased risk of developing a malignancy, is in Figure 5. This strategy includes a very careful clinical history and physical examination, as well as the performance of laboratory tests (mainly, a comprehensive serological screening), and CT scan of the chest to exclude ILD.

Limitations of the study

We acknowledge that our review may have some limitations. For instance, some studies considered in the analysis were retrospective case-control studies for which selection bias could not be excluded. Several of the included studies adopted different criteria for the diagnosis of paraneoplastic DM and/or considered different time periods before and after the diagnosis of DM for evaluation of the association with cancer.

Conclusions

However, in conclusion, the results of our comprehensive review of the literature and the meta-analysis have pointed out a subgroup of factors that would require particular clinical attention and that, taken together, should help clinicians in identifying DM patients that may be at increased risk of having or developing a malignancy.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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The Italian version of the systemic sclerosis questionnaire: a comparison of quality of life in patients with systemic sclerosis and with other connective tissue disorders

C. URAS 1, S. TABOLLI 1, P. GIANNANTONI 1, G. ROCCO 2, D. ABENI 1

Aim. Aim of the present study was to measure disability among patients with systemic sclerosis or other connective tissue disorders, using the specific Systemic Sclerosis Questionnaire (SySQ) and the Skindex-17.

Methods. Cross-sectional survey on hospitalized and day-hospital female patients in a dermatological setting, during March-May 2013. Comparison of disability and quality of life scores between patients in the two diagnostic groups.

Results. The use of these questionnaires in a clinical setting was well accepted. The levels of disability were slightly greater among women with systemic sclerosis in terms of general and musculoskeletal symptoms, while women with other connective tissue disorders had higher cardiopulmonary scores. The correlation between SySQ and Skindex-17 scores was low-moderate, indicating that the instruments indeed measure related but distinct constructs.

Conclusion. The Italian version of the SySQ may provide an additional tool for dermatologists, both in the research and clinical setting. Furthermore, its use may be extended to the medical as well as to the nursing clinical practice. Results from SySQ can be very useful for dermatological nursing-care for the implementation of educational plans targeted to patients, with the objective of enabling the patients to self-manage the disability of this severe chronic condition also outside of the strictly clinical setting.

Key words: Scleroderma, systemic - Connective tissue diseases - Disability evaluation - Quality of life.

The connective tissue diseases (CTD) constitute a group of chronic, inflammatory, immuno-mediated diseases which cause extensive tissue damage with frequent involvement of internal organs, and in particular of the respiratory system. Rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis (PM), dermatomyositis (DM), Sjogren’s Syndrome, and systemic lupus erythematosus (SLE) are among the most significant connective tissue diseases seen in the clinical units of dermatological institutes.

Systemic sclerosis is a multi-system disorder which affects the connective tissue and results in a generalized thickening of the skin, internal organ involvement, weakening of microcirculation, and of musculoskeletal tissue. Symptoms may vary greatly, depending on the degree of involvement of the skin and of the other affected organs.

Like many chronic conditions that impose a lifelong presence and concern to the patients, SSc, as well as other CTD, is associated with depression, a worsening of the quality of life (QoL) and physical disabilities.

In the recent past, disability among patients with SSc has been assessed using the Health Assessment Questionnaire (HAQ), which is not exhaustive, and sufficiently specific when measuring functional limitation in people affected by connective tissue disorders.

Therefore, there is a need for a tool to comprehensively measure the level of physical disability for patients affected by SSc, both in discriminative terms (i.e., in order to distinguish cross-sectional differences between patients with different levels of...
disability) and evaluative terms (i.e., to measure the change in physical disability during the course of the illness as the disease progresses and as it modifies due to on going treatment).

Such a tool could be useful both in the clinical routine as well as in the clinical research setting, since it could be utilized for the screening and identification of the specific areas on which to focus the diagnostic investigations and then the specific therapeutic interventions, monitoring both the progression of the condition and the possible effect of treatment.

Furthermore, tools of this kind could be useful for dermatological nursing purposes, as they would allow to identify specific issues of care, due to physical disability, so that it would be possible to propose interventions to improve the patients’ well-being and also to increase patients’ ability for self-care.

In our study we use the Italian version of a questionnaire designed to measure disability among patients with SSc, the Systemic Sclerosis Questionnaire (SySQ), with the joint objective to evaluate and compare the disability level among women with SSc or other CTD.

Materials and methods

This study is part of a larger project to evaluate the degree of disability among patients with CTD and to test educational activities aimed at reducing, or slowing down, the progression of such disabilities.

The study protocol was approved by the Institutional Ethical Committee of IDI-IRCCS.

Study population

During the period March-May 2013 we consecutively enrolled in this study 115 patients with SSc (ICD-9-CM code 710.1), and 35 with other connective tissue diseases (ICD-9-CM codes 710.0 and 710.2 through 710.9). This latter group was composed of systemic lupus erythematosus (SLE), dermatomyositis, and undifferentiated connectivitis, who were hospitalized either in the dermatological wards or were seen in the outpatient or the day-hospital clinics of IDI-IRCCS in Rome, Italy, were invited to participate in this study.

Inclusion criteria were: a diagnosis of connective tissue disease according to the criteria of the American College of Rheumatology, ability to read and to understand the Italian language, 18 years of age or older, signing the written informed consent form.

Gender was not an inclusion/exclusion criterion; however, during the study period, only two males had been seen who had agreed to participate in the study, so that the decision was made to limit the study to women.

Data collection

Socio-demographic characteristics (i.e., age, education, and marital status) were self-reported by the patients. Organ involvement and duration of disease were also self-reported, and were then cross-validated by nurses who abstracted information from the clinical records.

Questionnaires

The SySQ is a self-administered questionnaire that evaluates several aspects of the patients’ experience with the disease: functional disability, organ involvement, and general conditions.

It is composed of 32 items, each scored 0-3, with a possible total score ranging from 0 to 96. However, the original paper as well as a preliminary analysis on the psychometric properties of the Italian version, indicates that the more meaningful scores are those of the four main categories of the questionnaire: general symptoms, musculoskeletal symptoms, cardiopulmonary symptoms, and upper gastrointestinal symptoms.

The score for each category is obtained by summing the scores for all items pertaining to the same category. Higher values indicate worse disability.

The Italian version of the SySQ is reproduced in Appendix 1.

We also used a dermatology-specific questionnaire, to better describe the burden of disease deriving from skin involvement, and to study the relationship between the disease-specific and this specialty-specific instrument.

The Skindex-17 is a dermatology-specific health-related QoL instrument that was derived from the Skindex-29 using Rash analysis. It consists of 17 items, and the answers are given on a three-point scale. The answers options are: never, rarely/sometimes, often/always. The answers are scored on two scales, one for the symptoms and the other for the psychosocial domain. The scores of each scale
can be also categorized, with cut-offs at 50 for the symptoms (i.e., thus subdividing the scale in “mild-moderate” vs. “severe” impact) and 21 and 38 for the psychosocial scale (i.e., thus subdividing the scale in “mild”, “moderate”, and “severe” impact). Higher values indicate worse QoL on both scales.

The evaluation of the clinical severity of the disease was assessed using the Physician Global Assessment (PGA). It consists of a 5-point scale about diseases severity, with scores ranging from 0 to 4, corresponding to very mild, mild, moderate, severe, very severe. Due to the scarce numerosity in each of the five classes the PGA was dichotomized into “mild-moderate” and “severe”.

Translation of the SySQ

The Italian translation of the SySQ was conducted from the original German version using also the English version provided by the authors in the original paper. The translation/adaptation process was conducted according to the guidelines for the process of cross-cultural adaptation of patient-reported outcomes.

Statistical analysis

Descriptive analyses were conducted with standard statistical methods and tests, using the STATA statistical package, Release #9. For the categorization of the symptoms and psychosocial scales of the Skindex-17 we utilized the cut-offs published in the original validation paper. For the single-item analysis of the SySQ we dichotomized each item, separating the “lower impairment levels” (i.e., answers coded as “0” and “1”) from the “higher impairment levels” (i.e., answers coded as “2” and “3”).

Results

We collected data on 150 patients, 115 with SSc and 35 with CTD. This latter group was composed of SLE (3 patients), dermatomyositis (3), and undifferentiated connectivitis (29). The patients, as specified in the Methods section, were all females. The age range was 23-83 years, with a mean age of 58 years (standard deviation [SD] 1.4 years). The mean duration of the disease was 8.6 years (SD, 0.63 years).

Table I summarizes the main characteristics of the study population, also showing separately the characteristics of the two diagnostic groups under study.

Overall, it is interesting to note that while the dermatologists classified as severe or very severe only 17.9% of all patients, we observed only 16% of the study population without internal organ involvement, and approximately 50% of the women were in the “Severe” category of both scales of the Skindex-17.

As for the general socio-demographic characteristics, only few differences were observed between the women with SSc and those with other CTD: SSc patients were more likely to have a lower educational level (P value=0.042), and they had a longer disease duration (P value=0.045). A slight difference was observed in the clinical disease severity, as assessed by the physician: 20.3% of patients with SSc were classified as severe, compared to only 9.4% of the women with other CTD. However such difference did not reach statistical significance, due to the small number of patients with CTD.

In Table II we provide a comparison between patients with SSc or CTD, for all the levels of all the variables of interest, summarizing the mean values of the General Symptoms category of the SySQ and of the Symptoms scale of the Skindex-17 questionnaire. In general, average scores, both for the SySQ and the Skindex-17, tend to be higher among women with SSc compared to those with CTD, although very seldom such differences reach, or even come close to, a statistically significant level.

For the SySQ it is interesting to note that the levels of impairment are higher for women with internal organ involvement, and that the scores are progressively higher with the number of organ-systems involved. Also of interest, is that practically no differences are seen – for both women with SSc or CTD – according to the dermatologist’s evaluation of the clinical severity.

We also looked at the psychosocial scale of the Skindex-17, and here we noticed the same pattern with a few notable exceptions: among patients with a disease duration >10 years the impairment was much higher among women with CTD (70.8 vs. 38.9 for women with SSc), and this was also true for women without comorbidities (53.1 for CTD patients vs. 27.7 for SSc patients).

In Table III we summarize the mean scores and the 95% confidence intervals for the Categorical Scales and all the Subscales of the SySQ, to compare such scores between SSc and CTD patients. Also when
considering these summary scores, women with SSc have in general a slightly greater level of impairment than women with the other CTD. Such differences are more evident in the General Symptoms Category, but they also relevant for the Musculoskeletal Category and for the Eating subscale. The only exception, although without scales reaching statistical significance, is that women with CTD tend to have higher scores in the Cardiopulmonary Category as well as in the two Subscales of this category (i.e.,

<table>
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<tr>
<th>Variables</th>
<th>Overall N. 150</th>
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<th>P value</th>
</tr>
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<tr>
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<td></td>
<td></td>
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<td></td>
</tr>
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<td>44</td>
<td>31</td>
<td>13</td>
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<tr>
<td>50-64</td>
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<td>39</td>
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<td>37.1</td>
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<td>65+</td>
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<tr>
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<td>31</td>
<td>4</td>
<td>11.4</td>
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<td>Middle or high school</td>
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<td>48.6</td>
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<tr>
<td>College or higher</td>
<td>64</td>
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<td>35</td>
<td>15</td>
<td>42.9</td>
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<tr>
<td>Duration of illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 years</td>
<td>48</td>
<td>38</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>3-9 years</td>
<td>57</td>
<td>38</td>
<td>19</td>
<td>55.9</td>
</tr>
<tr>
<td>10+</td>
<td>41</td>
<td>36</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>Number of organ-systems involved</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24</td>
<td>19</td>
<td>5</td>
<td>14.2</td>
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<tr>
<td>1</td>
<td>35</td>
<td>25</td>
<td>10</td>
<td>28.6</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>46</td>
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<td>28.6</td>
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<tr>
<td>3</td>
<td>35</td>
<td>25</td>
<td>10</td>
<td>28.6</td>
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<tr>
<td>Organ involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiorespiratory No</td>
<td>59</td>
<td>45</td>
<td>14</td>
<td>40.0</td>
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<tr>
<td>Yes</td>
<td>91</td>
<td>70</td>
<td>21</td>
<td>60.0</td>
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<tr>
<td>Gastrointestinal No</td>
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<td>67</td>
<td>22</td>
<td>62.9</td>
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<tr>
<td>Yes</td>
<td>61</td>
<td>48</td>
<td>13</td>
<td>37.1</td>
</tr>
<tr>
<td>Musculoskeletal No</td>
<td>50</td>
<td>41</td>
<td>9</td>
<td>25.7</td>
</tr>
<tr>
<td>Yes</td>
<td>100</td>
<td>74</td>
<td>26</td>
<td>74.3</td>
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<tr>
<td>Skindex-17 symptoms</td>
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<tr>
<td>Mild-moderate</td>
<td>70</td>
<td>53</td>
<td>17</td>
<td>56.7</td>
</tr>
<tr>
<td>Severe</td>
<td>64</td>
<td>51</td>
<td>13</td>
<td>43.3</td>
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<tr>
<td>Skindex-17 psychosocial</td>
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<tr>
<td>Mild</td>
<td>33</td>
<td>25</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>Moderate</td>
<td>36</td>
<td>28</td>
<td>8</td>
<td>26.7</td>
</tr>
<tr>
<td>Severe</td>
<td>65</td>
<td>51</td>
<td>14</td>
<td>46.6</td>
</tr>
<tr>
<td>Physician Global Assessment</td>
<td></td>
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<td></td>
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<tr>
<td>Mild-moderate</td>
<td>119</td>
<td>90</td>
<td>29</td>
<td>90.6</td>
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<tr>
<td>Severe</td>
<td>26</td>
<td>23</td>
<td>3</td>
<td>9.4</td>
</tr>
</tbody>
</table>

Totals may vary because of missing values
Shortness of breath and Upper airway involvement).

In Figure 1 an example of single-item analysis is shown, regarding the General Symptoms Category. Each bar represents the percentage of women, in the two disease groups, who have reported for that question a higher impairment level, i.e., have answered with a score of either “2” or “3”. The questions about the extremities, and in particular those regarding the hands, are the ones that show a greater proportion of “higher impairment”. This proportion is almost invariably more substantial for women with SSc compared to those with CTD.

In Figure 2 we use the same approach to illustrate the results about selected items from the three other main Categories of the SySQ. In this case, the proportion of women with higher impairment is overall lower, but the differences are sharper for the items of the Musculoskeletal and Upper Gastrointestinal categories, with a higher impairment for the women with SSc. Also of note, is the confirmation that for

<table>
<thead>
<tr>
<th>Variables</th>
<th>SySQ General Symptoms</th>
<th>Skindex-17 Symptoms</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>SSc N.=115</td>
<td>CTD N.=35</td>
</tr>
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<td>Overall</td>
<td>1.43 1.25</td>
<td>0.130</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>&lt;50</td>
<td>1.89 1.22</td>
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<td>50-64</td>
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<td>65+</td>
<td>1.42 1.24</td>
<td>0.539</td>
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<td>Education</td>
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<td>Elementary</td>
<td>1.61 0.07</td>
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<td>Middle or high school</td>
<td>1.76 1.30</td>
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<td>College or higher</td>
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<td>Married</td>
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<td>&lt;3 years</td>
<td>1.34 1.48</td>
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<td>3-9 years</td>
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<td>10+</td>
<td>1.55 1.55</td>
<td>0.993</td>
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<td>Number of organ-systems involved</td>
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<td></td>
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<td>0</td>
<td>1.30 1.08</td>
<td>0.591</td>
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<td>1</td>
<td>1.20 1.15</td>
<td>0.855</td>
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<td>2</td>
<td>1.46 1.37</td>
<td>0.741</td>
</tr>
<tr>
<td>3</td>
<td>1.72 1.32</td>
<td>0.129</td>
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<td>Organ involvement</td>
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<td>Cardiorespiratory No</td>
<td>1.29 1.11</td>
<td>0.423</td>
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<tr>
<td>Yes</td>
<td>1.53 1.35</td>
<td>0.339</td>
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<tr>
<td>Gastrointestinal No</td>
<td>1.36 1.18</td>
<td>0.318</td>
</tr>
<tr>
<td>Yes</td>
<td>1.55 1.38</td>
<td>0.504</td>
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<td>Musculoskeletal No</td>
<td>1.27 1.28</td>
<td>0.988</td>
</tr>
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<td>Yes</td>
<td>1.52 1.24</td>
<td>0.089</td>
</tr>
<tr>
<td>Physician Global Assessment</td>
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<tr>
<td>Milde-moderate</td>
<td>1.45 1.28</td>
<td>0.306</td>
</tr>
<tr>
<td>Severe</td>
<td>1.44 1.21</td>
<td>0.569</td>
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</tbody>
</table>
Table III.—Mean scores, and 95% confidence intervals, for the categorical scales and the 12 subscales of the SySQ: comparison between scores of patients with SSc and patients with other CTD.

<table>
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<tr>
<th>Categorical scales</th>
<th>SSc N.=115</th>
<th>CTD N.=35</th>
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<tr>
<td></td>
<td>Mean</td>
<td>CI 95%</td>
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<tr>
<td>General symptoms</td>
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<td>1.30 -1.60</td>
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<td>Pain</td>
<td>1.45</td>
<td>1.29-1.61</td>
</tr>
<tr>
<td>Stiffness</td>
<td>1.15</td>
<td>1.01-1.30</td>
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<tr>
<td>Coldness</td>
<td>1.61</td>
<td>1.44-1.78</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>0.80</td>
<td>0.68-0.92</td>
</tr>
<tr>
<td>Complex function</td>
<td>0.79</td>
<td>0.65-0.93</td>
</tr>
<tr>
<td>Strength of hands</td>
<td>0.93</td>
<td>0.80-1.06</td>
</tr>
<tr>
<td>Rising</td>
<td>0.56</td>
<td>0.43-0.69</td>
</tr>
<tr>
<td>Walking</td>
<td>0.79</td>
<td>0.66-0.93</td>
</tr>
<tr>
<td>Cardiopulmonary symptoms</td>
<td>0.75</td>
<td>0.64-0.85</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>0.88</td>
<td>0.75-1.01</td>
</tr>
<tr>
<td>Upper airway</td>
<td>0.59</td>
<td>0.49-0.70</td>
</tr>
<tr>
<td>Upper gastrointestinal symptoms</td>
<td>0.78</td>
<td>0.66-0.89</td>
</tr>
<tr>
<td>Eating</td>
<td>0.94</td>
<td>0.80-1.10</td>
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<tr>
<td>Swallowing</td>
<td>0.51</td>
<td>0.39-0.63</td>
</tr>
<tr>
<td>Heartburn/regurgitation</td>
<td>0.88</td>
<td>0.74-1.02</td>
</tr>
</tbody>
</table>

Figure 1.—Single-item analysis for the General Symptoms category of the SySQ: proportion of patients scoring “2” or “3”, separately for patients with SSc or CTD.
the General Symptoms, the Musculoskeletal, Cardiopulmonary, and Upper gastrointestinal systems), but also may give detailed insight when the subscales and the single items are analyzed.

Our cross-sectional survey indicates that disability and quality of life impairment are very common in dermatological patients with SSc and CTD. Our results are in accordance with previous reports, where in particular the general and musculoskeletal symptoms 3 were found to have the higher impact on the disability, specially among women with SSc. Such impairment, for instance coldness and pain in the hands, has a direct impact daily activities such as cutting food, getting dressed, wash and dry on- self, etc. In turn, disability has an effect on quality of life, and in a very general way we notice that higher levels of disability on the SySQ may correspond to higher scores on the Skindex-17.

However, while such correlation exists, it is of a low-to-moderate level, usually in the 0.3-0.4 range the Cardiopulmonary category the women with CTD have a greater proportion of “higher impairment”.

The Italian version of the questionnaire, with the complete list of items and the appropriate response modality, is shown in Appendix 1. The solid horizontal lines separate the four main Categories; the dotted lines separate the twelve subscales. The sequence of the subscales is in the same order as they are listed in Table III.

### Discussion

In our study we have shown the feasibility to use in a clinical setting a specific instrument for the standardized measurement of disability among women with SSc or other CTD. The SySQ provides a quantitative assessment of important issues in these diseases, and allows a comprehensive evaluation at the level of the main categories of involvement (such as the General Symptoms, the Musculoskeletal, Cardiopulmonary, and Upper gastrointestinal systems), but also may give detailed insight when the subscales and the single items are analyzed.

Our cross-sectional survey indicates that disability and quality of life impairment are very common in dermatological patients with SSc and CTD. Our results are in accordance with previous reports, where in particular the general and musculoskeletal symptoms 3 were found to have the higher impact on the disability, specially among women with SSc. Such impairment, for instance coldness and pain in the hands, has a direct impact daily activities such as cutting food, getting dressed, wash and dry oneself, etc. In turn, disability has an effect on quality of life, and in a very general way we notice that higher levels of disability on the SySQ may correspond to higher scores on the Skindex-17.

However, while such correlation exists, it is of a low-to-moderate level, usually in the 0.3-0.4 range.

Figure 2.—Single-item analysis for selected items of musculoskeletal, cardiopulmonary, and upper gastrointestinal categories of the SySQ: proportion of patients scoring “2” or “3”, separately for patients with SSc or CTD.
for the correlation coefficients, indicating that the two instruments are indeed measuring different constructs, and that the skin manifestations – as measured by the Symptoms scale of the Skindex-17 – may only be a component of the wider problems encountered by the patients.

In fact, we should also consider that the Skin-17 is intended to measure the skin-related QoL of patients, whereas the SySQ is oriented to assess the level of physical disability and limitation. Moreover, the Skindex-17 is a specialty-specific instrument, targeted to patients with any dermatological disease, whereas the SySQ is a questionnaire specifically designed for patients with scleroderma. In the light of such results and considerations, it would seem advisable to use both instruments to achieve a really comprehensive description of the experience of each patient in their illness.

The acceptability of the Italian version of SySQ confirms, as it was true for the original study of Rouf *et al.*, that it is a good tool in assessing the level of disability in patients with systemic sclerosis, but also for patients with other connective tissue conditions. The Italian version of the SySQ did not show substantial differences between patients in the two clinical diagnostic groups of scleroderma or CTD. In fact, scores in each of the variables we considered were comparable for the SSc and the CDT. However, when looking at the subscales, differences emerged, specially for the categories of the General and of the Musculoskeletal symptoms, for which there seems to be a worse disability in patients with scleroderma. This finding could be explained by the fact that the General Symptoms category includes items assessing pain, stiffness, and coldness of extremities, and that these characteristics are more extremely pronounced in patients with scleroderma. This supports also the construct validity of the SySQ.

Interestingly, patients with systemic sclerosis were classified as having a higher clinical severity, according to the PGA, and the scores are significantly higher for the Skindex-17, but not for the SySQ: this could be due to the fact that the clinicians assessing the global situation of the patients were dermatologists, so that their evaluation might have been somewhat driven by the level of skin involvement – and this would be reflected, as noted above, by the two different natures of the SySQ and the Skindex-17. Furthermore, when looking at the PGA of women with SSc, again there is little difference in SySQ scores between patients with “mild-moderate” or “severe” clinical severity, while the difference is more marked in the Skindex-17 symptoms score for these two groups. This observation is also in line with the previous reports of a certain level of discrepancy between the way clinicians and patients evaluate the actual impact of skin diseases on patients.

Finally, it is interesting to note that the Skindex-17 scores in this sample are quite similar to those previously reported by our group, confirming the measurements obtained from this instrument are quite stable even when different groups of patients, enrolled in different clinical settings (e.g., outpatients vs. inpatients) and in different time-periods, are considered.

Conclusions

The Italian Version of the SySQ may provide an additional tool for dermatologists, both in the research and clinical setting. As stated in a recent editorial, accurate and comprehensive measures of clinical phenomena provide dermatologists and nurses with tools that should help them improve the quality of their care. The SySQ could be used for an initial assessment of the patient and for the follow up, in clinical studies or during the treatment of the SSc. In both cases it will allow the evaluation and the monitoring of the patients’ disability and the possible influence of treatment and general care on the progression of the disease. Results from SySQ could also be useful for dermatological nursing-care in guiding the implementation of educational plans targeted to patients, with the objective of enabling the patients to self-manage the disability of this severe chronic condition also outside of the strictly clinical setting.

References


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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Appendice 1

QUESTIONARIO SULLA SCLEROSI SISTEMICA

Questo questionario ha lo scopo di misurare quanto la sua malattia l’abbia condizionata nel corso dell’ULTIMA SETTIMANA. Per favore scegli con una crocetta una sola risposta a ogni domanda.

<table>
<thead>
<tr>
<th>Item</th>
<th>Modalità di risposta</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Con che frequenza ha sentito dolore alle mani nell’ultima settimana?</td>
<td>A</td>
</tr>
<tr>
<td>2. Nell’ultima settimana, quanto le facevano male le dita delle mani quando toccava o stringeva un oggetto?</td>
<td>B</td>
</tr>
<tr>
<td>3. Nell’ultima settimana, quanto erano rigide le sue braccia?</td>
<td>B</td>
</tr>
<tr>
<td>4. Nell’ultima settimana, quanto erano rigide le sue gambe?</td>
<td>B</td>
</tr>
<tr>
<td>5. Con che frequenza ha sentito freddo alle mani nell’ultima settimana?</td>
<td>A</td>
</tr>
<tr>
<td>6. Nell’ultima settimana, se aveva le mani fredde, quanto le facevano male le mani?</td>
<td>B</td>
</tr>
<tr>
<td>7. Nell’ultima settimana, se aveva i piedi freddi, quanto le facevano male i piedi?</td>
<td>B</td>
</tr>
<tr>
<td>8. Nell’ultima settimana, riusciva a tagliare la carne con il coltello?</td>
<td>C</td>
</tr>
<tr>
<td>9. Nell’ultima settimana, è stato/a in grado di lavarsi e di asciugarsi da solo/a?</td>
<td>C</td>
</tr>
<tr>
<td>10. Nell’ultima settimana, è stato/a in grado di mettersi le calze da solo/a?</td>
<td>C</td>
</tr>
<tr>
<td>11. Nell’ultima settimana, è stato/a in grado di spalmarsi sulla pelle le creme (e/o le pomate) da solo/a?</td>
<td>C</td>
</tr>
<tr>
<td>12. Nell’ultima settimana, è stato/a in grado di aprire e chiudere i rubinetti dell’acqua?</td>
<td>C</td>
</tr>
<tr>
<td>13. Con che frequenza ha sentito debolezza alle mani quando prendeva in mano un oggetto nell’ultima settimana?</td>
<td>A</td>
</tr>
<tr>
<td>14. Con che frequenza le sono caduti di mano degli oggetti nell’ultima settimana?</td>
<td>A</td>
</tr>
<tr>
<td>15. Nell’ultima settimana, è stato/a in grado di alzarsi da una sedia senza braccioli?</td>
<td>C</td>
</tr>
<tr>
<td>16. Nell’ultima settimana, è stato/a in grado di sdraiarsi e alzarsi dal letto da solo/a?</td>
<td>C</td>
</tr>
<tr>
<td>17. Nell’ultima settimana, è stato/a in grado di camminare su un percorso in pianura?</td>
<td>C</td>
</tr>
<tr>
<td>18. Nell’ultima settimana, è stato/a in grado di fare le scale a piedi?</td>
<td>B</td>
</tr>
<tr>
<td>19. Nell’ultima settimana, le mancava il fiato quando camminava per strada?</td>
<td>B</td>
</tr>
<tr>
<td>20. Nell’ultima settimana, le mancava il fiato quando faceva le scale a piedi?</td>
<td>B</td>
</tr>
<tr>
<td>21. Nell’ultima settimana, le mancava il fiato quando si vestiva?</td>
<td>B</td>
</tr>
<tr>
<td>22. Quanto ha tossito nell’ultima settimana?</td>
<td>B</td>
</tr>
<tr>
<td>23. Quanto ha espellitato nell’ultima settimana?</td>
<td>B</td>
</tr>
<tr>
<td>24. Nell’ultima settimana, ci sentiva incapace di far entrare aria nei polmoni?</td>
<td>C</td>
</tr>
<tr>
<td>25. Nell’ultima settimana, è (o sarebbe) stato/a in grado di mangiare una mela?</td>
<td>C</td>
</tr>
<tr>
<td>26. Nell’ultima settimana è (o sarebbe) stato/a in grado di mangiare bocconi di cibo abbastanza grandi?</td>
<td>A</td>
</tr>
<tr>
<td>27. Nell’ultima settimana ha provato difficoltà a “mandare giù” il cibo?</td>
<td>A</td>
</tr>
<tr>
<td>28. Nell’ultima settimana ha provato dolore quando “mandava giù” il cibo?</td>
<td>A</td>
</tr>
<tr>
<td>29. Nell’ultima settimana, quando “mandava giù” il cibo, le si fermava in gola?</td>
<td>A</td>
</tr>
<tr>
<td>30. Nell’ultima settimana, ha sentito bruciore alla bocca dello stomaco?</td>
<td>A</td>
</tr>
<tr>
<td>31. Nell’ultima settimana, ha avuto rigurgiti?</td>
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**Modalità di risposta- A**

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<td>Mai</td>
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**Modalità di risposta- B**

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<tr>
<td>Per nulla</td>
<td>Poco</td>
<td>Molto</td>
<td>Moltissimo</td>
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**Modalità di risposta- C**

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<tbody>
<tr>
<td>Senza difficoltà</td>
<td>Con poca difficoltà</td>
<td>Con molta difficoltà</td>
<td>Non in grado di farlo</td>
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Cutaneous involvement in case of lupus erythematosus (LE) is very frequent and can present both specific or non-specific manifestations. LE specific lesions can be classified in acute, subacute and chronic cutaneous LE lesions. All of them can be localized and generalized. The LE non specific lesions are not exclusive to LE disease but are often seen in patients with active systemic LE. All the cutaneous lesions are often induced or aggravated by ultraviolet light, in fact they are usually localized in sun-exposed areas. Acute cutaneous LE is associated with systemic disease, subacute cutaneous LE has been considered a subset of its own since 1979 when it was first described, chronic cutaneous LE is the most common subtype of LE. Although less frequently also the chronic cutaneous lesions can be an aspect of systemic LE (25%).

**Key words:** Lupus erythematosus, cutaneous - Skin diseases - Autoimmune diseases.

Lupus erythematosus (LE) is a chronic autoimmune disease characterized by cutaneous and systemic symptoms. According to Gilliam and Sontheimer cutaneous lesions can be divided into two groups: LE-specific and LE-non specific lesions. LE-specific skin manifestations have a typical histopathological picture with interface changes. LE-specific lesions can be subdivided into acute cutaneous LE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE) where discoid LE is the most common form. Among CCLE, lupus erythematosus tumidus (LET) has been described, even though some authors include LET as a separate subgroup called intermittent subtype of CLE (ICLE). The LE-non specific lesions are not exclusive of LE and include a wide range of symptoms with different histopathological findings.

**Chronic LE**

Discoid LE is the most common form of chronic LE (CLE). The lesions are erythematous maculae or plaques with a hyperkeratotic surface (Figure 1). These plaques grow peripherally into larger plaques that heal with atrophic scars and pigmentary changes in particular of the external edges. Often keratin accumulates in the hair follicle and when peeled back, a keratotic spike can be seen protruding from the under surface of the scale (carpet-tack sign). The lesions are localized above the neck in 60-80% of cases (localized DLE, L-DLE) and below the neck in 20-40% of cases (disseminated DLE, D-DLE), usually on the trunk. Mucosal discoid lesions are also frequent 25%. They are asymptomatic and are characterized by a violaceous erythema with white striae. Also the lower lip can be involved with erythema and striae. Mutilations with tissue loss can be seen especially when the lesions affect the ears and the tip of the nose (Figure 3). In some patients the keratotic aspect is very important (verrucous DLE) or the lesions appear nodular (hypertrophic DLE). Very rarely some...
Comedo-like lesions can be present on the discoid skin manifestations (lupus comedonicus) (Figure 3). When the lesions are localized on the scalp on hairy areas a cicatricial alopecia develops (Figure 4). The 70-80% of patients suffer from photosensitivity. A recent study has shown that 17% of DLE patients receive a diagnosis of systemic LE (SLE) during the following three years from the development of cutaneous lesions.

Lupus erythematosus tumidus (LET) is characterized by erythematous-edematous skin manifestations without hyperkeratosis and atrophic scars. The lesions most commonly involve the face and 80% and more of the patients suffer from photosensitivity (Figure 5).

Lupus profundus is a panniculitis where the inflammation is primarily located in the lower dermis and subcutaneous tissue. The UV exposure seems to be of minor importance in this subset. The lesions are subcutaneous nodules which develop chronic deep scars (Figure 6).

Subacute cutaneous LE

It was described by Gilliam and Sontheimer and has been considered as a subset of its own
since 1979. This form is more common in Caucasian, the majority of patients (90%) is photosensitive and the lesions are located on the upper back, shoulders, dorsal part of the arms; less frequently face and scalp are involved. Two groups of lesions are described: a psoriasiform and an annular form. In the psoriasiform form, papulosquamous lesions resembling psoriasis are present (Figure 7), in the annular form, erythematous plaques or papules which become widespread annular and polycyclic clearing centrally are seen (Figure 8). The combination of these two forms is possible. SCLE is strongly associated with the anti-Ro/SSA antibodies. About 20% of SCLE patients present other types of CLE lesions and about 50% fulfill the American College of Rheumatology criteria for SLE. About 1/3 of all SCLE cases, particularly those diagnosed in older ages, can be attributed to previous drug exposure (non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, anti epileptic, terbinafine, TNF-α inhibitors and diuretics).

**Acute CLE**

It is usually associated with systemic disease. The most common lesion is malar rash or butterfly erythema. It is a typical localized lesion with erythema and edema over the malar eminence and the nose with a tendency to spare the naso-labial folds (Figure 9). Postinflammatory hyperpigmentation can occur, on the contrary, scars never develop. An exanthematic generalized form of acute CLE can occur and is localized on the trunk. All the lesions are usually associated with a previous sun exposure. Typically, patients
are critically ill due to SLE and present underlying manifestations in various organs, as well as high titers of antinuclear antibodies, frequently anti-dsDNA antibodies. Mucosal involvement is usual. Most often the buccal mucosa is involved with erosions of the lower lip and palatal mucosa, clinically different from the lichenoid aspect of DLE. Hair loss is one of the most common cutaneous signs of SLE. Alopecia can be the presenting manifestation of SLE and may affect the scalp, eyebrows, eyelashes, beard and body hair. Sometimes it can occur or be aggravated because of the medications used to treat lupus. Acute lupus alopecia is usually non scarring and it is characterized by diffuse hair loss or by sparse thin hairs (lupus hair) with clusters of newly regrown hairs.18

**LE non-specific lesions**

They are diagnosed in about 45-50% of the LE patients, in particular in SLE patients. The most fre-
and arms, but the face and other areas of the body may also be affected. Bullous SLE is a subepidermal blistering disorder that primarily affects young women. This form responds dramatically to Dapsone. The lesions are widespread vesicobullous lesions that heal without scarring. Mucosal involvement is relatively common. Histologically it is characterized by subepidermal blisters with neutrophilic infiltrate in the dermal papillae (Figure 11). The basement membrane split is located below the lamina densa and often anti type VII collagen (non-collagenous domain) antibodies but no antinuclear antibodies are detected.

Conclusions

LE is characterized by a wide range of cutaneous lesions which occur in about 85% of the patients. In SLE they represent the first sign of the disease in about 30% of the patients. Cutaneous lesions are important for providing information about the diagnosis and prognosis of the disease, in fact discoid or tumidus LE lesions are usually associated with a non-systemic disease, on the contrary malar rash, cutaneous mucinosis or vasculitis are an aspect of systemic lupus. However, any cutaneous lesions deserve attention as lupus is, in some cases, a severe disease.

References

9. Cozzani E, Christana K, Rongioletti F, Rebora A, Parodi A. Lupus erythematosus tumidus: clinical, histopathological and serologi-
Cutaneous manifestations of systemic lupus erythematosus


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Hair disorders are frequently observed in various systemic diseases, including autoimmune connective tissue diseases (CTDs), with predilection of lupus erythematosus (LE), followed by dermatomyositis (DM) and scleroderma. Hair disorders in CTDs may manifest as various clinical patterns, such as telogen hair loss, diffuse thinning or fragility of hair, and scarring alopecia. Less common hair disorders include anagen effluvium, alopecia areata, and trichomegaly. Some drugs used to treat CTDs may cause hair loss in a drug-related manner or hypertrichosis. In the assessment of common hair loss patterns, such as telogen effluvium, the possible association with CTDs must be borne in mind and should not be overlooked. Alopecia appears to be a significant sign in the course of LE and especially systemic LE. In DM, the involvement of the scalp is common, and is often characterized by a diffuse, violaceous, scaly, non-scarring and symptomatic hair loss. Linear scleroderma en coup de sabre is an uncommon localized form of morphea with involvement of the paramedian forehead and frontal scalp, where it is associated with cicatricial alopecia. The most important variant of scarring alopecia in the context of CTDs is that associated with discoid lupus erythematosus (DLE). In the diagnostic work-up of DLE-related cicatrical alopecia, histopathological and immunopathological studies are useful, and a relevant role has been attributed to dermatoscopy (trichoscopy) over the last years. Hair loss has been reported in several other CTDs, including mixed and undifferentiated CTDs, and primary Sjögren’s syndrome, although it is likely to be underestimated in such diseases.

**Key words:** Hair diseases - Alopecia - Lupus erythematosus, cutaneous - Dermatomyositis - Scleroderma, diffuse - Connective tissue diseases.

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noncicatricial subtypes, apart from very few exceptions. In an international survey of SLE, malar rash (40%), alopecia (24%), and oral ulcers (19%) were the most frequent cutaneous signs. Skin lesions found to be associated with a worse prognosis include photosensitivity, oral ulcers, Raynaud’s phenomenon, and alopecia. In a cohort of patients with early undifferentiated CTDs, those who evolved to SLE were more likely to have alopecia and discoid lupus, along with other clinical and immunological criteria. In general, clinical studies in SLE patients have shown that alopecia is more frequent in women. In a Chinese study, adult-onset SLE male patients, when compared with adult-onset females, presented more frequently with discoid rash, but less frequently with alopecia. A lower prevalence of alopecia has been repeatedly confirmed in SLE patients with late onset of the disease (beyond the age of 50 years). In SLE, alopecia tends to be less common in children than in adults. A lower frequency of alopecia was detected in patients with subacute cutaneous LE compared to patients with chronic cutaneous LE. However, alopecia has been reported in several other CTDs, including mixed and undifferentiated CTDs, and primary Sjögren’s Syndrome. The prevalence of hair disorders in such diseases is likely to be underestimated, also considering the relative paucity of specific clinical and epidemiological studies on this topic in CTDs other than LE. For instance, considering our routine experience, primary Sjögren’s syndrome can have an association with telogen effluvium, especially in cases with extra-glandular manifestations, and less frequently with cicatricial alopecia secondary to lichen plano-pilaris, but large studies are needed to test and verify these hypotheses.

In this article, special attention will be focused on the most important hair disorders associated to CTDs, with a revision of general, clinical and diagnostic aspects, and with special emphasis on LE-related hair disorders. Cicatricial alopecia and telogen effluvium will be discussed more in depth because of their frequency and relevance. The diagnostic methodology of hair loss consists of multiple steps, depending on the clinical form, and may take into account physical and dermatoscopic examination of the scalp and hairs, the assessment of hair density, the pull test, the wash test, the modified wash test, and, in selected cases often represented by cicatricial alopecia, scalp biopsy and histopathology. In the assessment of common hair loss patterns, such as telogen effluvium, the possible association with CTDs must be borne in mind and should not be overlooked.

### Scarring alopecia

Scarring alopecia or cicatricial alopecia is the result of the irreversible damage of hair follicles with the obliteration of follicular orifices and progressive replacement with fibrous tissue responsible for permanent hair loss. The degree of damage and fibrosis of this disfiguring disease is variable among patients according to the intensity of the offending process. The most paradigmatic examples of cicatricial alopecia are represented by lichen plano-pilaris and discoid LE (DLE).

In certain systemic diseases, permanent destruction of hair follicles may be caused by blood supply abnormalities, direct compression, or release of proinflammatory cytokines. These events may take place, for example, in sarcoidosis, systemic amyloidosis, and scleroderma. Scarring alopecia has infrequently been reported in DM. The typical DM-related hair loss is in fact non-cicatricial, but it may overlap with the scarring alopecia of other CTDs, particularly scleroderma and LE.

Other mechanisms that potentially, even if rarely, can lead to cicatricial damage and largely involve patients with SLE are immunologically mediated vasculitic lesions or microthrombotic vasculopathic lesions triggered by procoagulant and/or hyperviscosity states associated with LE (antiphospholipid antibody syndrome). Such lesions may be characterized by either a severe pandermal vasculitis with thrombosis and cutaneous infarction, or luminal thrombi occluding vessels in the reticular dermis or subcutis with necrosis of the epidermis and dermis, with a compensatory dilatation of superficial vessels. When the vasculitic or vasculopathic processes are limited, however, the resulting injury might result in reversible and non-scarring hair loss.

Linear scleroderma “en coup de sabre” is an uncommon localized form of morphea with onset typically in childhood or adolescence. It generally presents as a dyschromic, atrophic, linear depression located on the paramedian forehead and frontal scalp, where it is associated with cicatricial alopecia. It can present with more than one lesion, typically following Blaschko’s lines.
ly distinguishable from other forms of scleroderma. The histopathology of alopecia in linear morphea is characterized by dense dermal sclerosis with marked reduction in the number of follicular units and with atrophy of eccrine and sebaceous glands. In earlier lesions, an intense infiltration of lymphocytes and plasma cells, extending deeply into the reticular dermis up to the subcutis and even to the fascia, has been described, sometimes with a perineural distribution. On histopathology, the atrophic follicular remnants in linear scleroderma were found to have morphologic aspects similar to those observed in chemotherapy-induced permanent alopecia but not in alopecia secondary to morphea or other cicatricial alopecias.

Scarring alopecia associated with chronic cutaneous discoid lupus erythematosus

Cicatricial alopecia associated with DLE is reported as a LE-specific skin lesion in the Gilliam classification, as it shows LE-specific histologic features. According to the provisional classification for primary cicatricial alopecia created in 2001 by the North American Hair Research Society, alopecia caused by DLE is included among the primary acquired lymphocytic scarring alopecias and is considered to be the most common form in this group.

Cicatricial alopecia is a frequent complication of DLE and is estimated to occur in at least one third of patients with DLE, showing correlation with a prolonged disease course. Scalp may be the only area affected in approximately 10% of DLE patients. Scalp DLE affects women more often than men. Progression to systemic involvement with SLE is described as an uncommon event in DLE patients with isolated involvement of the scalp. Scalp DLE is present in up to 14% of patients with SLE, and can often be the presenting manifestation of SLE.

In LE, the injury of hair follicles, as well as that of other target structures, is mediated by inflammatory immune mechanisms, recruiting T cells, cytokines, autoantibodies, and immune complexes. Among the major proinflammatory events implicated in DLE and related scarring alopecia, there are type I interferon-associated cytotoxic inflammation, loss of hair follicle immune privilege, and loss of immunosuppressive signals. Like other cicatrical alopecias, there is the permanent damage to the pluripotent hair follicle stem cells in the bulge area of hair follicles, and the loss of the sebaceous gland is a frequent associated finding. In scalp DLE, a relevant role for the induction of the inflammatory response has been attributed to the Langerhans cells, whose infundibulocentric distribution below the entry of the sebaceous glands into the follicle corresponds to the pattern of mid-follicular inflammation involving the follicular bulge that is typically revealed by the histopathological examination of lesional skin.

In cutaneous LE, the antigenic stimulus triggering the immune response is thought to be ultraviolet radiations, although this hypothesis may be hardly adapted to the hair-bearing scalp, a site relatively protected from the sunlight. Interestingly, patients with concomitant androgenetic alopecia were found to be less prone to develop DLE lesions in bald areas, possibly because of the depletion of immunogenic target structures. Mechanical stimuli, such as intense rubbing and scratching, thermal injury, or infection can favor the occurrence of new lesions in affected patients. Koebner phenomenon may also arise from other dermatoses, such as contact dermatitis, infection, or even after hair transplantation (Figure 1). However, the relation of exposure to the offending stimulus (e.g., ultraviolet radiations) with the development or exacerbation of lesions can be not easily recognized because of the lag time between the events. Smoking has been shown to have a pronounced influence on cutaneous LE, and appears also capable of diminishing the effectiveness of antimalaria.
Clinically, early DLE lesions present as scaling erythematous or violaceous papules or well-demarcated, erythematous, oval or roundish patches with adherent follicular hyperkeratosis. Later, the lesion progresses centrifugally to form a nummular (discoid) white ivory, atrophic, depressed plaque with follicular plugging and adherent scale. Telangiectasias are usually present. After removal of the adherent scale, which can be difficult and painful, keratotic spikes corresponding to the follicular plugging can be seen (“carpet tack” sign). The acronym PASTE has been created to summarize the key clinical features: plugging, atrophy, scale, telangiectasia, and erythema. Lesions may sometimes be pruritic or tender, although they are often asymptomatic and, at the most, when symptoms are complained, they are usually of mild-to-moderate severity. Pigmentary changes may be observed especially in darker-skinned individuals, with hypopigmentation in the central area and hyperpigmentation at the periphery of the patches. In a study performed in 36 patients with DLE scarring alopecia, 33.3% presented a single lesion and 52.7% presented multiple lesions, while 13.8% exhibited a picture resembling pseudopelade of Brocq.

Squamous cell carcinoma has been described as a rare late sequel in chronic lesions. A lichen plano-pilaris and LE overlap condition has been recently described in a male presenting with frontal fibrosing alopecia, in whom biopsies from the scalp and other sites demonstrated features consistent with lichen plano-pilaris, but direct immunofluorescence studies showed a positive lupus band test.

DLE-related alopecia is usually irreversible if not treated early to control the inflammatory process and to prevent the damage of the stem-cell-containing midfollicle area. Classic treatment includes topical, systemic or intralesional corticosteroids, and topical calcineurin inhibitors, but antimalarial drugs, thalidomide, oral cyclosporin and sulfones may be active as well. Oral isotretinoin can be also considered for refractory cases. Other therapeutic options are gold, methotrexate, mycophenolate, azathioprine, and cyclophosphamide.

**Diagnostic aspects**

As concerns differential diagnosis, DLE scalp lesions must be differentiated by a large variety of cutaneous disorders, such as alopecia areata, lichen plano-pilaris, tinea capitis, morphea, early phases of squamous cell carcinoma, and actinic keratoses (Figure 2).

In the diagnostic work-up, the initial approach should include the assessment of the entire scalp and a complete physical examination in order to detect other cutaneous or systemic pathological signs, such as the presence of discoid lesions elsewhere or other LE-related features. Histopathological and immunopathological studies are helpful in confirming the diagnosis. Two biopsy specimens, one for standard hematoxylin-eosin sections and the other for direct immunofluorescence, should be taken. Ideally, two distinct biopsies can be performed for standard histopathology, one examined for transverse sectioning and one for vertical sectioning. Punch or excisional scalp biopsy specimens should be obtained from the border of early clinically active lesions (anyhow from inflammatory areas), and extend into the fat, avoiding to choose end-stage cicatricial areas which are likely to provide nonspecific and useless findings.

The major histopathologic features found in active scalp DLE lesions are: follicular hyperkeratosis, epidermal atrophy, superficial and deep patchy interstitial and periadnexal lymphocytic infiltrate, thickened basement membrane, basal vacuolar degeneration at the dermal-epidermal junction, mucin deposition in the papillary dermis, and extravasation of red blood cells.

![Figure 2.—A patient with diffuse scalp DLE lesions (resembling actinic keratoses) in association with alopecia areata.](image)
cells around the inflamed blood vessels. In the late stages, fibrosis and a reduction of pilosebaceous units are characteristic findings.\textsuperscript{43, 50} Direct immunofluorescence reveals deposition of immunoglobulins (most frequently IgG) and C3 in a granular or homogeneous band-like pattern at the interface between the dermis and the follicular epithelium or the epidermis.\textsuperscript{1} A study demonstrated that histopathology alone was able to support a correct diagnosis only in 68.5\% of cases; in the other cases, the diagnosis was made through the additional evaluation of immunopathologic findings.\textsuperscript{43} In the final phase, in the absence of clinically evident inflammatory signs, alopecic patches can be difficult to differentiate from alopecia areata or pseudopelade of Brocq. On histopathology, these lesions usually lack superficial inflammation, but show deeper inflammation with perifollicular lymphocytic infiltrates or infiltrates within fibrous tracts. In the late-stage pseudopelade-like lesions, the absence of hair follicles and fibrosis are detected.\textsuperscript{23}

In the last years, dermoscopy (dermatoscopy) has become a popular diagnostic method among dermatologists, and may represent a relevant diagnostic tool not only for pigmentary skin lesions but also for other skin conditions. Trichoscopy, or dermoscopy and videodermoscopy of the scalp, may shows features of a specific pattern of hair loss.\textsuperscript{51, 52} Dermoscopic examination may be useful to guide scalp biopsy in scarring alopecia, allowing the selection of the optimal biopsy site.\textsuperscript{53} In cicatricial alopecia, trichoscopy can reveal reduced hair density and loss of follicular openings. Dermoscopic findings associated with scalp DLE include: scattered dyschromia, follicular plugs, telangiectasias, and irregularly distributed blue-gray dots in a speckled pattern between the hair follicles, and in more advanced stages, fibrosis-related white central plaques and milky-red areas, along with a reduced number of follicular ostia.

Follicular keratotic plugs are a marker of DLE and correlate with follicular hyperkeratosis and plugging of the ostia with keratotic material.\textsuperscript{54} Moreover, scalp DLE may be differentiated from lichen plano-pilaris thanks to the presence of follicular red dots (Figure 3), that are erythematous, polycyclic, concentric structures, regularly distributed around the follicular ostia.\textsuperscript{55} These dots are present in active DLE and seem to be a good prognostic factor for hair regrowth. Among the characteristic trichoscopic features of DLE of the scalp, there are particular types of yellow dots, that correspond to hyperkeratotic plugs, and are different from those classically observed in alopecia areata. In scalp DLE, in fact, yellow dots are large and surrounded by radial, thin arborizing vessels emerging from the dot, arranged as a “red spider in yellow dot”.\textsuperscript{56} Long-lasting, inactive DLE lesions differ from active lesions by the presence of structureless milky-red areas, and lack of follicular orifices.\textsuperscript{52, 56}

As concerns the multiple blue-grey dots, they correspond histopathologically to melanophages in the papillary dermis. This finding results from interface dermatitis and the subsequent pigment incontinence, and may be associated also with lichen plano-pilaris. However, some authors highlight some possible peculiarities in the distribution pattern of such dots, described as “speckled” in DLE, and as a “target” pattern in lichen plano-pilaris.\textsuperscript{57} In the latter case, there is a circular arrangement around the follicular structures and follicular white dots, thus preserving the interfollicular epidermis.

**Non-scarring alopecia**

*Lupus erythematosus*

The skin findings in cutaneous LE have been divided into two groups, LE-specific and LE-non-
specific skin changes. Biopsy of LE-specific skin lesions shows LE-specific histology, as happens in DLE, thus permitting the confirmation of LE diagnosis, while LE non-specific skin lesions are not histopathologically distinct for LE and/or may be seen as a feature of another disease process.

Non-scarring alopecia is included among LE-non-specific skin disorders in the modified Gilliam classification of LE-related skin lesions and seems to be very frequently encountered in SLE patients, especially during the active phases of the disease. Diffuse, non-scarring hair loss can be the presenting manifestation of SLE. Polyarthralgia, fever and hair loss have been mentioned as the most common presentation of SLE in some reports. This clearly highlights the importance of hair loss as a diagnostic clue of LE. Hair loss may affect not only the scalp, but also eyebrows, eyelashes, beardhair, or body hair.

A study in Pakistani patients with SLE specified the association with non-cicatricial diffuse alopecia in 22% of patients. In an Italian case series, non-scarring alopecia was observed in 31% of SLE patients, usually in the active phases of the disease. A cross-sectional study tried to identify cutaneous manifestations that could be used as a marker of systemic involvement in LE. A highly significant association was found between SLE and non-scarring alopecia, while no significant association was noted between SLE and scarring alopecia.

There are several etiologies for the non-cicatricial alopecia, as already declared in the modified Gilliam classification, but the main types correspond to lupus hairs, telogen effluvium, and alopecia areata. Telogen effluvium, which will be examined in depth in a distinct paragraph, is likely to be the predominant non-scarring alopecia associated with LE.

An interesting pilot study analyzed the dermoscopic and histopathological features of diffuse non-scarring hair loss in four women suffering from SLE. Scalp dermoscopy showed scaling, perifollicular telangiectasia, increased numbers of short vellus hairs, focal atrichia, and decreased hair shaft pigmentation. Of note, scalp tissue histopathology revealed typical changes of LE. These preliminary results seem therefore to suggest that non-scarring alopecia in SLE might sometimes display more LE-specific findings than expected.

In a prospective, multicenter European study, clinical and laboratory characteristics were examined in 1002 patients with different subtypes of cutaneous LE: acute cutaneous LE, subacute cutaneous LE, chronic cutaneous LE, and intermittent cutaneous LE. LE-nonspecific skin lesions were diagnosed in 45.2% of patients with cutaneous LE, with the most frequently reported manifestation being diffuse alopecia (55.8%). Diffuse alopecia was recorded significantly more often in patients with chronic cutaneous LE and acute cutaneous LE than in patients with subacute cutaneous LE or intermittent cutaneous LE.

Another form of transient alopecia in chronically active SLE patients is the so called “lupus hairs”, which consist in thin, dry, weakened hairs, especially at the periphery of the scalp, with possible evident recession. Lupus hairs have been substantially related to telogen effluvium, although the true telogen hair loss is generally more extensive, and overlap between the two entities exists. It is hypothesized that the hair growth disruption in this circumstance is due to the induction of a negative nitrogen balance.

A possible variant of non-scarring alopecia seldom encountered consists in a band-like alopecia along the posterior occipital and temporal margins, resembling the ophiasis pattern of alopecia areata.

Another hair loss pattern that is considered fairly common and important in SLE patients, despite the relatively scarce number of literature reports, is patchy, non-cicatricial alopecia. This form of hair loss seems to occur in patients with severe disease. In a cross-sectional study of 122 SLE patients, the overall prevalence of non-scarring patch alopecia was 14.8%. In patients who experienced hair loss after SLE diagnosis, non-scarring diffuse hair loss was the most common pattern (65.1%) followed by non-scarring patchy alopecia (15.1%). In patchy non-cicatricial hair loss, there are scattered patches of partial hair loss, with mild erythema and without scarring. Gentle traction reveals that hairs remaining in the alopecic patches are almost all telogen hairs, or dystrophic anagen hairs. SLE-associated non-scarring patchy alopecia should be carefully differentiated from alopecia areata. Histopathological features are similar to those shown in alopecia areata, with peribulbar infiltrate of lymphoid cells surrounding anagen hair bulbs, many of which are miniaturized. The diagnosis of LE might be suggested by the greater density of inflammatory infiltrate, presence of dermal mucin, and further clinical and
HAIR DISORDERS ASSOCIATED WITH AUTOIMMUNE CONNECTIVE TISSUE DISEASES

CASSANO

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Dear authors,

Serological findings. For the differential diagnosis, dermatoscopy may be successfully used, as demonstrated by a recent study. While exclamation-mark hairs, black dots, broken hair and yellow dots are helpful for diagnosis of alopecia areata, common dermoscopic features in SLE patchy alopecia were hair shaft thinning and hypopigmentation, telangiectasias, peripilar sign, perifollicular red dots, white dots and honeycomb pigment patterns. Interfollicular polymorphous vessels were the most common vascular pattern in the SLE alopecia patches.

In exceptional cases, non-scarring hair loss in LE may derive from vascular lesions of mild severity when they are not capable of irreversible damage and spare the stem cell-rich follicular area. Other histopathological substrates described in anecdotal cases of LE patients with non-scarring alopecic patches are lupus panniculitis and tumid lupus (papulo-nodular mucinosis). The literature also contains a report of a lupus panniculitis of the scalp occurring along Blaschko’s lines and presenting as a reversible linear alopecia.

Non-scarring alopecia is usually responsive to treatment of the lupus, and hair regrowth is expected after LE is well controlled and becomes quiescent, although some drugs usually used to treat lupus can cause hair loss.

Dermatomyositis

In DM, the involvement of the scalp is common and can be the presenting manifestation. It usually manifests as diffuse, confluent, erythematous to violaceous, atrophic, scaly plaques, resembling seborrhoeic dermatitis or psoriasis, and can be often misdiagnosed. Unlike lupus, the eruption is frequently accompanied by intense pruritus or burning. Hair loss tends to be diffuse, although it is often more subtle than in LE. This diffuse, violaceous, scaly, non-cicatricial symptomatic alopecia is one of the typical cutaneous signs of DM, without being pathognomonic, especially in patients with adult-onset classic DM and amyopathic and/or hypomyopathic DM, in whom it can accompany a disease flare. Non-cicatricial hair loss has also been observed in juvenile-onset DM. In case series, scalp involvement has been recorded in 63-82% of DM patients, and alopecia in 33-43%.

Histopathology and dermoscopy can be helpful, especially when differential diagnosis with psoriasis or psoriasiform dermatitis is not possible. Histopathological changes can be similar to those detectable in lupus and comprise epidermal atrophy, basement membrane degeneration, vacuolar changes in the basal keratinocytes, and a perivascular lymphocytic infiltrate, which is less abundant and less deep than in lupus. Accumulation of mucin usually in the papillary dermis can be seen. Direct immunofluorescence can show deposition of immunoglobulin at the dermal-epidermal junction, but of less intensity than in lupus.

As concerns serologic studies, circulating antibodies targeting melanoma differentiation-associated gene 5 (MDA5), an antigen involved in innate immune responses also named CADM-140, have been identified in DM patients with little or no myositis and with an increased risk of interstitial lung disease. Patients with anti-MDA5 antibodies also were found to have an increased risk of arthritis/arthralgia and some cutaneous manifestations, including diffuse hair loss.

According to some authors, scalp DM is a treatment-resistant disease, even when other cutaneous lesions of DM show clinical response.

Special forms of non-scarring alopecia

Telogen effluvium

It is well known that the hair follicles have an intermittent activity, known as hair cycle, characterized by an ever-ending sequence of phases of growth (anagen), involution (catagen), and rest (telogen). In the scalp, telogen usually lasts for up to 3 months, catagen only a few weeks, while the anagen phase duration, which influences the hair length, is estimated to be 2-7 years. Normally, up to 90% of hair follicles on the human scalp are in anagen, 10-14% are in telogen and 1-2% in catagen. A latency period may occur between hair shedding (teloptosis, exogen) and the early emergence of the next anagen VI stage. Exogen corresponds to the programmed termination of telogen hair and finishes with its shedding (teloptosis). Kenogen indicates the physiological interval of the hair cycle in which the hair follicle remains empty after the telogen hair has been extruded and before a new anagen hair emerges.

Telogen effluvium is due to an abnormally high number of hairs entering the telogen phase simul-
taneously with loss of the usual asynchrony in normal hair loss. The consequent hair loss may vary in severity with daily shedding of more than 100 hairs even up to 300 hairs. Different pathomechanisms resulting in telogen hair loss have been recognized: a) immediate anagen release, with premature start of telogen after 2-3 months from a triggering event; b) delayed anagen release caused by the prolongation of anagen (i.e., postpartum hair loss or discontinuation of contraceptive pill); c) immediate telogen release (i.e., shortening of telogen, sometimes observed at the beginning of therapy with minoxidil); d) shortened anagen (idiopathic shortening of anagen duration, leading to mild persistent hair loss and inability to grow the hair long); e) delayed telogen release (prolonged telogen and delayed transition to anagen, which can be responsible for seasonal shedding in humans). 80 Rebora has recently proposed a simplified classification of telogen effluvium categorizing three main mechanisms: a) premature te-loptosis; b) collective teloptosis; c) premature entry into telogen. 19 This last form can be further distinguished according to the etiology into three subcategories: medications, dietary deficiencies, and lymphotoxicity (autoimmunity).

Telogen effluvium is considered the most common form of hair loss seen in systemic disease. 81 A short-lived insult usually produces a sudden onset of diffuse shedding, after time interval of 2-3 months. This can be associated to physiologic stress, severe illness, or drug-induced hair loss. When the insult is prolonged or repeated, shedding can develop insidiously. Chronic telogen effluvium refers to telogen hair shedding persisting longer than 6 months. A shortening of anagen is the mechanism most commonly involved. Recently, chronic telogen effluvium has been related to a reduction in the variance of anagen duration. 82

Chronic telogen effluvium has been distinguished into an idiopathic form and chronic diffuse telogen hair loss secondary to a variety of organic causes. To be a true cause of chronic diffuse telogen hair loss, the relationship between the trigger and the disease has to be reversible and reproducible. Common causes of chronic diffuse telogen effluvium are thyroid disorders, profound iron deficiency, malnutrition, and treatment with some drugs (e.g., retinoids and cytotoxic drugs). 80 SLE and DM are included among the documented causes of chronic diffuse telogen hair loss. 83 In SLE and other similar systemic inflammatory conditions, the telogen effluvium is thought to derive from both severe catabolic effects and the action of high levels of proinflammatory cytokines during disease flare on hair growth cycling. 23 The “autoimmune” telogen effluvium, recently described by Rebora, 19 actually corresponds to an exogen effluvium, and is characterized by a sudden onset and intermittent course. This condition has been called “autoimmune” because of the common coexistence of circulating anti-thyroperoxidase antibodies and full-blown Hashimoto thyroiditis, as it happens in alopecia areata. Other less frequent associations reported by the authors are other thyroid autoimmune disorders, and other autoimmune diseases, such as Sjögren’s syndrome, in accordance with our clinical experience. Moreover, it should be mentioned that autoimmune thyroid diseases have in turn a significant association with various other autoimmune disorders, including primary Sjögren’s syndrome, rheumatoid arthritis, SLE, systemic sclerosis and DM. 84

The hair loss in telogen effluvium occurs in a diffuse pattern. Trichodynia is frequently complained and has been described as a possible marker of disease activity corresponding to the presence of an active inflammatory peripilar process. 85 86 On examination, the scalp appears nonerythematous and without remarkable changes, and the hair appears normal in thickness. The absence of signs of hair miniaturization can be easily confirmed by dermoscopy, allowing the differentiation from androgenic alopecia. Bitemporal thinning can be present along with a marked regrowth of smaller hair in the frontal and bitemporal areas. Hair pull test is commonly positive, with many hairs coming out easily from their roots, with an elongated hair bulb visible to the naked eye. 21 80 The modified wash test can be a simple and useful diagnostic tool. 19

Differential diagnoses comprise androgenic alopecia, alopecia areata incognito, and other causes of non-scarring alopecia.

ANAGEN EFFLUVIUM

Anagen effluvium results from an abrupt cessation of the metabolic and mitotic activity of the follicular epithelial compartment is rapidly suppressed. 23 87 Dramatic hair loss occurs shortly after the insult, within days or weeks. Although anagen effluvium is
commonly associated with chemotherapy and radiation to the head and neck, other causes of anagen effluvium are: severe protein energy malnutrition, pemphigus vulgaris, and exposure to toxic agents and some medications. Certain inflammatory diseases are also capable of diminishing the metabolic activity of hair follicles, resulting in anagen effluvium. The paradigmatic case is represented by alopecia areata, in which the anagen arrest is the consequence of an autoimmune T cell-mediated insult against hair follicle antigens. Occasionally, patients with severe systemic disease, such as secondary syphilis and SLE, may experience dystrophic anagen effluvium. In such diseases, an anagen arrest occurs through the development of peribulbar inflammation, and a temporary shutdown of the hair matrix, analogous to Beau’s lines in the fingernails.23

**Alopecia areata**

Alopecia areata is known to be associated with atopic and autoimmune disorders, and has been recorded in a small percentage of patients with rheumatoid arthritis, SLE, scleroderma, and other CTDs.88, 89 An increased incidence of alopecia areata was revealed in patients with LE.88 A significant association between LE and alopecia areata was recently confirmed by a nationwide population-based study from Taiwan.90 Figure 2 shows a case of coexistence of alopecia areata and DLE.

**Drug-induced hair disorders**

Some drugs used to treat CTDs (i.e., azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, gold) may cause hair loss in a drug-related manner.91, 92 The medication-induced hair loss is usually diffuse, non-scarring, and limited to the scalp. Women are more commonly affected than men.92 Systemic retinoids, occasionally used in the treatment of cutaneous LE, may cause reversible alopecia, hair greying and hair curling/kinking.23, 91, 92 Antimalarial therapy has long been recognized as a cause of hair depigmentation and graying, especially in people with blonde or reddish hair.23, 93 Hypertrichosis is a well-established side effect of cyclosporine, topical and systemic corticosteroids, and has been also reported with methotrexate and penicillamine.91

**References**

HAIR DISORDERS ASSOCIATED WITH AUTOIMMUNE CONNECTIVE TISSUE DISEASES

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Cutaneous malignancies have been significantly associated with autoimmune connective tissue diseases (ACTDs). This review focuses on the current state of knowledge on skin cancer risk in the most prevalent ACTDs in dermatology including lupus erythematosus, scleroderma, dermatomyositis and Sjögren syndrome. Potential pathogenetic mechanisms for the association between ACTDs and malignancy involve disease-related impairment of immune system, sustained cutaneous inflammation, drug-associated immune suppression and increased susceptibility to acquired viral infections. An additional causal role might be played by environmental factors such as UV exposure and smoking. The occurrence of skin cancer can have a profound impact on the already compromised quality of life of ACTD patients. Therefore, effective screening and monitoring strategies are essential for ACTD patients as early detection and prompt therapeutic intervention can reduce morbidity and mortality in these patients.

**Key words:** Connective tissue diseases - Lupus erythematosus, cutaneous - Skin diseases - Carcinoma, squamous cell.

Malignancies have been widely reported as co-morbidities of autoimmune connective tissue diseases (ACTDs). Patients with ACTDs have an increased risk of secondary hematological malignancies and solid tumors including cutaneous malignancies, mostly non melanoma skin cancers (NMSC), melanoma and lymphoma.1-6

ACTDs are polygenic clinical disorders of unclear etiology with heterogeneous and overlapping features characterized by abnormal immune system activity and autoimmunity, leading to tissue inflammation. The most prevalent ACTDs in dermatology include lupus erythematosus (LE), scleroderma, dermatomyositis and Sjögren syndrome (SS). An increased risk of skin cancer might be expected in ACTDs patients due to the prevalence of ACTDs in the population, the long disease duration and the improved care and life expectancy of patients.1

Skin cancer is a multistep process and, as such, many events can contribute to its occurrence in ACTDs. Impaired immune system, mainly due to active disease and ACTD-associated immune dysfunction, seems to be one of the major risk factors for cancer. Similarly, chronic cutaneous inflammation, hallmark of ACTDs, is likely to contribute directly to the pathogenesis of malignancy through increased susceptibility to cell mutagens and DNA changes.7 In addition, a number of drugs used for the treatment of ACTDs have been reported to increase the incidence of cutaneous malignancies, due to direct mutagenesis of DNA or iatrogenic-induced immunosuppression with interruption of immunosurveillance.2, 4, 6, 8 However, the role of these drugs is debated as their strong anti-inflammatory and disease-modifying properties slow down disease progression and, thus, may even have a favorable influence on the risk of malignancies. It may be also difficult to differentiate whether the increased risk of skin cancer is linked

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to disease-related or treatment-related immune dysfunction.² Patients with ACTDs may also exhibit a higher risk of infections because of treatment and underlying impairment of the immune system.⁹ Moreover, ACTD patients have greater exposure to infectious pathogens, owing to continuous seeking medical advice in outpatient and/or inpatient departments. Given the well-known oncogenic potential of several virus,¹⁰ an increased risk of infection in ACTD patients may, thereby, enhance the probability to develop skin cancer. Finally, common genetic and environmental background (UV exposure, smoking) for ACTDs and cancer may also play an additional role.¹¹

This review focuses on the current state of knowledge concerning the risk of skin cancer in the most common ACTDs seen in dermatological clinical practice.

**Lupus erythematosus**

A significantly elevated overall cancer risk has been reported in patients with LE compared to the general population.¹, ¹², ¹³ Squamous cell carcinoma (SCC) appears as the most frequent skin cancer in LE patients (Figure 1), although few cases of melanoma and basal cell carcinoma (BCC) have been described.¹, ¹², ¹⁴, ¹⁵

A Swedish population-based study evaluated the association between systemic LE (SLE) and malignancy in 5715 patients identifying 443 cancer cases. SLE patients were shown to be at increased risk of SCC (standardized incidence rate [SIR] = 1.53, 95% CI 0.98-2.28), which was more pronounced after more than 15 years of follow-up.¹⁶ In a large study investigating the association between SLE and malignant diseases in an unselected cohort of Icelandic patients, SCC was the only individual cancer type to be statistically increased with an observed/expected ratio of 6.43 (95% CI 1.31-18.5, P=0.012).¹⁷ The incidence of potentially virus-induced malignancies, mainly HPV-associated cancers, was investigated in 576 Danish patients with SLE. Twelve NMSC were diagnosed in 46 cancer patients confirming a higher risk for NMSC among SLE patients compared to the general population (SIR=2.0, 95%, CI 1.2-3.6).¹² In contrast to the abovementioned studies, in a Hungarian cohort, the SIR for skin cancer was significantly decreased in SLE patients (SIR=0.04, 95% CI 0.001-0.236).¹⁸

In a Swedish cohort of cutaneous LE (CLE) patients, 21 SCCs out of 183 incident cancers were observed in 3663 patients with a 4-fold higher risk of SCC in CLE patients compared to a control cohort from the general population.¹³ The general hazard ratio (HR) for SCC was 3.6 (95% CI 1.8-7.2) with greatest HR for the first year after CLE diagnosis (HR 5.2, 95% CI 1.3-21.1). The risk estimates remained elevated even after excluding patients also diagnosed with SLE (HR 2.8, 95% CI 1.2-6.2).

SCC is a well recognized complication of discoid LE (DLE) with an incidence ranging from 2.3% to 3.3%.¹⁹, ²⁰ More than 100 cases of SCC in DLE lesions have been described, mainly arising in longstanding lesions,¹³, ²¹ although cases of SCC can also develop in DLE plaques of recent onset.²², ²³ DLE-related SCC appears as solitary lesions, less frequently as multiple lesions, in sun-exposed skin areas with...
lips, forearms, back of hands, cheek and scalp being the preferential anatomic locations.\textsuperscript{24, 25} Interestingly, SCCs in DLE lesions have a more aggressive behavior compared to non DLE-related SCC with recurrence rates of 29\%, metastatic rates of 16\% and death ratios of 19.4\%.\textsuperscript{19, 24-26}

Concerning mechanisms linking LE with cutaneous malignancies, disease-related and/or treatment-related impairment of the immune system may play a significant role in cancer development. In DLE, predisposing factors are also related to chronic inflammation, scarring, actinically damaged epidermis and decrease in protective melanin at the lesion site.\textsuperscript{27} The role of sun exposure in the development of NMSC in LE is still debated: about two-thirds of LE patients have been reported to be photosensitive, such people should avoid the sun and have fewer NMSC.\textsuperscript{13} However, despite advice, they might not change their exposure habits and/or inappropriately use sunscreens. Therefore, additional environmental factors should be considered in LE as driving stimuli including HPV infection\textsuperscript{28-30} and tobacco use, in cases of SCC of the lips.\textsuperscript{23}

Surveillance bias may, to some extent, also explain the significantly increased occurrence of NMSC in the LE population, mainly during the first year after diagnosis, since they can be more readily diagnosed in patients subjected to close medical attention because of chronic disease.\textsuperscript{1, 12, 13}

\section*{Scleroderma}

Current evidences support an increased risk of malignancy in scleroderma patients compared to the general population, with an overall prevalence of 3.6-10.7\%.\textsuperscript{31} SCC is the most common skin cancer observed in scleroderma patients, mainly in patients with generalized or pansclerotic morphea, although all variants of scleroderma can be interested.\textsuperscript{32} Additional cutaneous neoplasia include melanoma, dermatofibrosarcoma protuberans and BCC.\textsuperscript{33-39} A Swedish national population-based study reported an increased risk of NMSC in scleroderma patients with a SIR of 4.2 (95\% CI 1.4-9.8), especially among women.\textsuperscript{40} Increased NMSC risk was limited to the subset of patients with diffuse or limited scleroderma. In a larger Danish population-based study, cancer was diagnosed in 222 out of 2040 sclerodema patients and comprised 28 NMSCs (BCC and SCC) and 6 melanomas with an increased risk of NMSC (SIR=1.3, 95\% CI 0.9-1.9), especially among men (SIR=2.4, 95\% CI 1.2-4.4), and of melanoma (SIR=1.7, 95\% CI 0.6-3.6) in the absence of gender difference.\textsuperscript{41} A SIR of 26.6 for NMSC was reported in a Hungarian cohort of 218 scleroderma patients.\textsuperscript{42} Nine melanomas out of 90 cancer cases were identified in 441 scleroderma patients of a population-based cohort from South Australia. In this study, NMSC could not be evaluated since they were not included in the registry.\textsuperscript{37}

Regarding clinical characteristics of scleroderma-related SCC, the current knowledge relies on isolated case reports or small case series.\textsuperscript{32, 38, 43, 44} It is well established that SCC can arise on chronically inflamed wounds and, as such, burns, scars and skin ulcers may precede malignant transformation. Since it is not uncommon for patients with scleroderma to develop ulcers and scars, it is conceivable that scleroderma patients have a high risk to develop SCC within these lesions. The most common reported sites of scleroderma-related SCC are legs followed by feet and scalp. Patients consistently suffer from scleroderma for years prior to developing a tumor and multiple primaries within confluent sclerotic plaques are a feature in adult onset cases.\textsuperscript{32} Finally, patients with scleroderma are likely to develop more aggressive SCC, probably due to a difficult and delayed recognition of the tumor at diagnosis since it arises in already damaged skin.\textsuperscript{38, 45, 46}

The increased risk of skin cancers in scleroderma may be related to the primary immune suppression of the disease itself or may be secondary to the immunosuppressive effect of therapies (drugs, UVA1 and PUVA therapy).\textsuperscript{41, 42} Since tumor location corresponds to sites commonly affected by fibrosis and ulceration, persistent inflammation, local lymphatic ablation, poor nutrient and vascular delivery at these sites may also facilitate the development of skin cancer in scleroderma patients.\textsuperscript{58}

\section*{Sjögren’s syndrome}

Lymphoproliferative malignancies are a well-established life-threatening comorbidity of Sjögren’s syndrome (SS). A high incidence of lymphomas, mainly B-cell lymphomas, has been reported in primary SS patients with an estimated 16-fold increased risk as compared to the general population.\textsuperscript{47-50} A
Dermatomyositis

The association between dermatomyositis (DM) and risk of malignancy has been extensively reported in epidemiological studies, occurring in about 30% of cases with a higher incidence in elderly individuals and within the first year of DM diagnosis.59-62 Cancer diagnosis can precede, parallel or follow DM diagnosis. The reported highest risk for cancer within the first year of DM diagnosis suggests the paraneoplastic nature of DM.61 However, a more aggressive cancer screening after the diagnosis of DM could influence detection of malignancy. A parallel clinical course between DM and malignancy has been reported in some patients, with disappearance of DM cutaneous and muscle manifestations after treatment of the tumor and recurrence of DM symptoms after recurrence of cancer. Although the underlying mechanisms of this association are unclear, it has been suggested that the presence of a cross-reaction between antigenic epitopes in the muscle and tumor antigens generate an inflammatory response against muscle.63 The lifelong use of immunosuppressive medications in DM may also contribute to an elevated risk of cancer after years of observation.

The types of malignancy detected in patients with DM generally reflect those found in age- and sex-matched general population, further supporting the paraneoplastic process in DM that can happen with any kind of cancer. Newly diagnosed patients with DM should receive age- and gender-appropriate malignancy evaluations although the optimal strategies and length of cancer screening are still a matter of debate.

Melanoma has been rarely reported in association with DM, mainly as metastatic disease. Occurrence of DM during the course of melanoma has been regarded as a poor prognostic marker leading to death of patients within a few months.64, 65 However, a more recent literature review revealed that DM occurring in patients with stage IV melanoma is associated with a poorer prognosis as compared to stage IV melanoma patients without DM while stage III melanoma patients with and without DM retain similar prognosis.66 In a single-center retrospective study assessing malignancies up to 12 months after the diagnosis of DM, 3 NMSCs (2 SCCs and 1 BCC) were identified out of 12 cancer cases in 139 newly diagnosed DM patients.60 However, few data are available on NMSC in DM patients, since data on NMSC are not included in all studies.67 Occurrence of cutaneous lymphomas has been exceptionally described in DM patients. Isolated reports of mycosis fungoides,68, 69 angiotropic T-cell lymphoma 70 or nasal type NK/T cell lymphoma 71 as well as of cutaneous B cell lymphoma have been described in patients with DM.72, 73

Final considerations

Patients with ACTDs exhibit a higher risk of developing skin tumors, especially SCC. The occurrence of skin cancer has a profound impact on their already compromised quality of life and their life ex-
pectancy. Awareness of this association can guide effective screening and monitoring strategies in ACTD patients since early detection and rapid therapeutic intervention can reduce morbidity and mortality. Continuing interest in this field may help to understand the underlying biological mechanisms linking skin cancer to ACTDs and, thus, to identify risk factors in such patients.

References


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Drug induction in connective tissue diseases

A. VERDELLI, E. ANTIGA, V. BONCIOLINI, D. BONCIANI, W. VOLPI, M. CAPRONI

Connective tissue diseases (CTDs) are defined as a group of acquired disorders resulting from persistent immuno-mediated inflammation. Several classes of drugs seem to be capable of inducing or exacerbating CTDs. A drug-induced (DI) syndrome is defined as a condition temporally related to continuous drug exposure, which resolves upon drug discontinuation. Among CTDs, lupus erythematosus is the most widely known and investigated DI syndrome. However, in recent years, the association between the onset of other CTDs, such as dermatomyositis (DM) and morphea/systemic sclerosis (SSc) has increased in patients with preceding exposure to particular substances. Herein, we conducted a review of published case reports including DM and morphea/SSc, evaluating the real causality among drugs and these syndromes.

Key words: Connective tissue diseases - Dermatomyositis - Scleroderma, systemic.

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Materials and methods

We carried out a review of the Medline/PubMed-cited literature on DI-DM and morphea/SSc until the 1950s. Regarding DM, we only included cases of classic and amyopathic DM, while cases of DI-PM were excluded.
Results

Drug-induced dermatomyositis

DM is a rare autoimmune disease characterized by proximal muscle weakness, elevated serum creatine kinase (CK), abnormal electromyogram and abnormal muscle biopsy.

Pathognomonic cutaneous findings include Gottron’s papules, Gottron’s sign and heliotrope rash. Until now, different DM subsets have been identified. These subsets include classic DM, amyopathic DM (without muscle involvement), hypomyopathic DM, post-myopathic DM and DM sine dermatitis.7

In the past, DM caused or exacerbated by drugs has also been described as drug-induced dermopathy, pseudo-DM, DM-like eruption or DM associated with a specific drug.

The search yielded 72 articles reporting a possible association of drugs with DM. We identified a total of 91 DI-DM reported cases.

DM was described both in male and female patients with no sex prevalence. The median age at diagnoses was 56 (ranging from 29 to 82 years). The median duration of treatment before the onset of DM was 24 months ranging from 2 days after a carticaine injection to 11 years in association to penicillin. The majority of patients had underlying disease (65%). Malignancies were present in 37 out of 91 patients (40%) and the most common one was chronic myelogenous leukaemia (CML). Other haematological disorders included: acute lymphocytic lymphoma, acute myeloid leukemia, follicular lymphoma, essential thrombocythemia, polycythemia vera and myelofibrosis.8-10 The neoplasms also included two cases of gastrointestinal adenocarcinomas 11, 12 and one case of melanoma which developed after interferon α-2b treatment.13

Autoimmune diseases were present in 22 out of 91 patients (24%). The most common one was rheumatoid arthritis (RA) (17 out of 22 patients)14-16 followed by juvenile idiopathic arthritis (JIA) 17, 18 and psoriasis.19, 20 In one case, DM developed in a patient treated with anti TNF-α for Crohn’s disease.21

A cytoreductive agent, hydroxyurea (HU), used in the treatment of neoplastic myeloproliferative disorders (chronic myeloid leukaemia, polycythemia rubra vera, essential thrombocytthemia and myelofibrosis), was the most common drug involved.8,10,22-34 Other medications such as D-penicillamine, non-steroidal anti-inflammatory drugs, anti-infective agents, anti-neoplastic, lipid lowering drugs and anti TNF-α have also been associated with DI-DM (Table I).35-65 For some of these agents, only sporadic or unique cases were reported.

Most of the patients showed clinical and histologic findings similar to those of the idiopathic form. However, compared with the other DI-DM,4 the HU-induced DM seems to be associated with a distinct dermopathy. The HU reaction had typical dermal features of dermatomyositis, like scaly erythematous patches, papules and plaques of the dorsal hands, with atrophic and telangiectatic changes. Pruritic erythematous patches developing on the extremities and dorsa of the feet, and poikiloderma in photosensitive areas have also been rarely described. The face may be involved, with edema and heliotrope rash in some cases.8

HU-induced DM cases were uniformly negative for systemic involvement, with no antinuclear autoantibodies (ANA)-positive patients. It was not reported any proximal muscle weakness and the muscle enzyme level and electromyography were normal. In most patients, clinical manifestations im-

Table I.—Drugs reported to be the trigger of drug-induced dermatomyositis.

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<th>Cytotoxics/antitumor antibiotics</th>
<th>Hydroxyurea</th>
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<td>HMG Co-A reductase inhibitor</td>
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<td>Simvastatin</td>
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<td>Chelator</td>
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<td>Local anesthetic (Amide)</td>
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<td>Phenylbutazone</td>
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<td>Proton pump inhibitor</td>
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<td>Sulfa antimicrobial</td>
<td>Sulphacetamide sodium10% eye drops</td>
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<td>Antimetabolite (5-fluorouracil)</td>
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<td>Alpha-blocker</td>
<td>Alfuzosin</td>
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<td>Fibrate</td>
<td>Gemfibrozil</td>
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<td>Vaccine</td>
<td>BCG vaccine</td>
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<td>Bisphosphonate</td>
<td>Zoledronic acid</td>
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<td>Tumor necrosis factor alpha</td>
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<td>inhibitor</td>
<td>Adalimumab</td>
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<td>Infliximab</td>
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proved within the 1 to 12 months that followed the discontinuation of HU therapy without recurrence.26

On the other hand, with ANA positivity (80%),4 the non-HU-DM commonly displayed muscle weakness or evidence of myositis The HU group had a longer time to onset (>5 years) and it was invariably associated with other cutaneous signs of HU therapy including: leg and oral ulcers, stomatitis, melanonychia, palmoplantar keratoderma and ichthyosiform lesions.28 As a result of these distinct features, DM induced by HU is most commonly termed HU-induced DM-LE, but has also been known as DM-like lesions, pseudo-DM, Gottron’s papules-like rash or HU dermopathy. Nofal et al recently proposed the term “HU-induced amyopathic DM” to identify this subset of patients because the skin lesions are identical to the one of classic DM, but without the clinical or laboratory evidence of myositis.

Several cases of statin-induced DM among non-HU-DM were described 35-38 These 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, commonly used in the treatment of hypercholesterolaemia and prevention of cardiovascular events, are known to produce a skeletal muscle myopathy with symptoms ranging from mild myalgias to frank rhabdomyolysis. In literature there are 14 reports of statin-associated DM mostly characterized by typical cutaneous lesions, elevated CK levels and proximal muscle weakness during or after statin therapy. DM manifested between 2 months and up to 5 years after the initiation of treatment. The disease occurred either after intake of first-generation (simvastatin, lovastatin and pravastatin) or of second-generation HMG-CoA reductase inhibitors (atorvastatin and fluvastatin).38 Apart from one fatal outcome due to DM-associated lung fibrosis, statin-associated DM shows a relatively benign course. However, most cases required systemic treatment with glucocorticoids to control the disease.36

In recent years, as anti-tumor necrosis factor (TNF)-α treatment has increased, especially in severe psoriasis, and side effects associated to this class of drug have increased. Anti- TNF-α associated DM/PM is rare, consisting in less than 1% of reported cases of anti- TNF-α induced autoimmune phenomena.39-44 We found 14 publications describing a total of 21 patients who were treated with anti-TNF-α agents in the setting of dermatological or rheumatologic conditions such as RA, Crohn’s disease, ankylosing spondylitis (AS), JIA and seronegative arthritis with a familiar history of psoriasis who developed DM. Anti-TNF-α therapy included etanercept, adalimumab, infliximab and lenercept. In two cases both infliximab and adalimumab were administered while in one case etanercept and adalimumab determined a new onset and an exacerbation of DM. An improvement of DM after withdrawal of the anti-TNF-α agents was recorded in more than 94% of cases.21

Drug-induced morphea/systemic sclerosis

The term scleroderma refers to thickening of the skin as a result of increased collagen deposition. It is classified as two separate, but related entities, a localized form and a systemic form.

The localized scleroderma, also known as morphea, is a sclerotic condition limited to the skin. It is divided into five categories: plaque, generalized, bullous, linear, and deep.66

SSc is a heterogeneous disease which pathogenesis is characterized by small vessel vasculopathy, production of autoantibodies and fibroblast dysfunction leading to increased deposition of extracellular matrix.67 The clinical manifestations and the prognosis of SSc vary with the majority of patients having skin thickening and variable involvement of internal organs. SSc is divided into limited and diffuse disease based on the extent of skin involvement.

In literature, there are various syndromes and anecdotal cases in which patients have features similar to, or the same as, those in “classic” scleroderma after being exposed to drugs.6

These syndromes can be triggered or exacerbated by many drugs such as taxanes, bleomycin, pentoxycine, D-pencillamin, anti-neoplastic agents, cathepsin K inhibitor balicatib, and injections (vitamin K1 e K12) (Table II).68-97 Recently, 4 cases of anti TNF-α induced morphea have also been reported. Two cases were associated to adalimumab, one to infliximab and the last one to etanercept.68-71

Totally, 82 cases of DI morphea/SSc were found. Patients’ median age was 40 years (ranging from 12 to 79 years) mainly female. Skin lesions appeared after a mean period of 12.5 months (from 1 to 36 months) after the beginning of the drug treatment which was believed to be responsible for the lesion development. Most reactions occurred during active treatment, but in few cases after the therapy was stopped.5,72,73
Most of the cases described showed morphea, characterized by oval or round areas of induration confined to the dermis, while a minority of the patients developed SSc, with confluent plaques involving different cutaneous sites and systemic involvement. Linear scleroderma was described only in children. In two cases bullous lesions were also present. Vitamin K1, vitamin B12 and pentazocine-induced morphea was always limited at site of injection. Sclerotic lesions were usually preceded by erythematous lesions, variably itchy or associated with tingling or burning sensation.

Many chemotherapeutic agents have been associated to scleroderma-like lesions. Currently, taxanes (docetaxel and paclitaxel) are the most common drugs involved. These antimicrotubule agents are widely used in the treatment of metastatic breast cancer and other solid tumors. In literature, a total of 16 cases of taxanes induced scleroderma were reported. The female prevalence can be explained by the frequent use of taxanes in the treatment of breast and ovarian cancer. In most patients, skin sclerosis developed mainly on the extremities, especially on the lower parts of the legs. In all the cases, oedema developed a few months before skin sclerosis, and appears to be one of the preceding factors for skin sclerosis itself. Systemic involvement including Raynaud’s phenomenon and pulmonary fibrosis, as well as immunological abnormalities, was not detected in any of the patients. The discontinuation of the drug was associated to oedema and sclerosis improvement, but steroids were necessary in most of the cases to control the disease.

So far, a total of 11 cases of bleomycin-induced scleroderma have been reported. Bleomycin, administered intravenously or intramuscularly, is an antitumor antibiotic with a mild myelosuppressive effect. It is used to treat several types of cancer, including testicular neoplasm, as well as Hodgkin and non-Hodgkin lymphoma. Pulmonary fibrosis is the most severe toxicity associated with belomycin injection. The cutaneous adverse reactions included erythema and infiltrations with marked hyperpigmentation. Nine out of 11 patients showed localized scleroderma while only 2 patients developed diffuse plaques. Sclerodactyly with swelling and induration of the hands and forearms was present in all the patients, while Raynaud’s phenomenon and digital pitting scar were described in few patients. ANA were detected in five cases, but no patients showed SSc-specific antibodies. Visceral involvement was reported only in two patients with lung damage. In many instances, withdrawal of the culprit drug was not sufficient to obtain complete remission, suggesting that the drug was the trigger exacerbating an underlying scleroderma.

Few patients with metastatic melanoma treated with interferon-alpha (INF-α), developed vitiligo and morphea or SSc. There have also been reports of cases in patients receiving pegylated INF-α combined with ribavirin for treatment of hepatitis C infection.

Nine patients treated with balicatib, an inhibitor of the osteoclastic enzyme cathepsin K under evaluation for the treatment of osteoporosis, developed dose related morphea-like lesions. Skin hardening affected mostly the trunk and the neck with diffuse morphea. No systemic involvement was detected and none of the patients showed Raynaud’s phenomenon. In only one case there was swelling of the fingers with parasthesia and slight sclerodactylty. ANA positivity was demonstrated only in four patients.

Finally, 17 patients under ergot treatment have
been reported with scleroderma and typical migraine headaches. Most of the patients developed stage I or II vascular scleroderma, Raynaud’s phenomenon and systemic involvement including pleural and myocardial damage.\(^6\)

For all the other drugs, only sporadic cases have been described with scleroderma-like lesions, usually in the limited variant. Interestingly, few cases associated with L-5-hydroxytryptophane and carbidopa showed hypereosinophilia with an eosinophilia myalgia-like syndrome.\(^94\)

**Discussion**

**Drug-induced dermatomyositis**

Several cases of DI-DM were described in the past decades. The majority of cases (85%) had pathognomonic skin findings for DM with or without muscle involvement, associated to compatible histology. Serologies, including ANA and anti-Jo1, were mostly negative.

The pathomechanism of DI-DM is not well understood yet. It is postulated that the main mechanisms, by which these drugs induce autoimmunity, are the promotion of apoptosis and the enhancement of the innate immune response. This causes the displacement of various cellular antigens resulting in a state of neo-antigenicity and anti-endothelial cell antibody formation.

**DI-morphea/SSc**

Different categories of drugs have been implicated in DI-scleroderma. In many cases, discontinuation of the culprit agent alone was not sufficient to obtain complete remission, suggesting that the drug was the trigger exacerbating an underlying scleroderma.

A direct role for some classes of drugs in the pathogenesis of scleroderma is well demonstrated. As an example, the bleomycin-induced mouse model has

**Table III.—** DI-DM: diagnostic criteria.

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<td>1. A plausible time relationship to drug administration</td>
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<td>2. No other concurrent disease or drugs that could have caused the DM</td>
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<tr>
<td>3. Remarkable improvement of the skin lesions after withdrawal (dechallenge)</td>
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<td>4. Reappearance of the skin lesions upon rechallenge</td>
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revision had underlying malignancies. The most common one was CML. In a recent review,\(^4\) evaluating a total of 70 DI-DM patients, authors pointed out that the presence of an associated disease alone, especially malignancy, may not provide a strong argument for the onset of DM in the majority of patients. DM occurred after a long period (> 3 years) and nearly in all patients there was an improvement of DM with discontinuation of the drug and/or additional treatment (84.3%).\(^30\) Moreover, adenocarcinomas, the most common DM associated malignancies \(^99\) were present only in two DI-DM patients. All these data suggest a possible pathogenetic role of these drugs in developing DM.

Recently, Seidler et al proposed a classification system for DI-DM composed of four criteria, shown in Table III. If all the 4 criteria were present DI-DM was considered certain. \(22\) of the suspected cases of DI-DM showed an association between DM and RA. Such an association has long been well known, but its real incidence is unknown.\(^40\) RA can precede myositis or it can develop after the diagnosis of DM.\(^39\) However, no uniform criteria or detailed case records can be found regarding these cases. Furthermore, patients with DM may also have joint manifestations that can be misinterpreted as RA, even if these manifestations rarely lead to joint deformities and destruction.\(^42\)

To our knowledge, there is no clear and confirmed relation between RA and DM, even if there is a significant increase in the frequency of autoimmune diseases (also including RA) in first-degree relatives of patients affected by idiopathic inflammatory myopathies. This association between many autoimmune diseases can be explained by the fact that many disorders share genes that together act as polygenic risk factors for autoimmunity.\(^98\)

In the whole, 40% of the patients reported in our
been established and used extensively to investigate the pathogenesis of SSc. It has also been used to seek new therapeutic agents, since the subcutaneous injection of bleomycin to mice induces fibrosis and inflammatory infiltration in the dermis and lung and stimulated autoantibody production, which mimics SSc.6

A profibrotic effect due to the collagen synthesis and/or fibroblast growth, has also been documented for peplomycin, dopaminergic drugs and beta-blocker agents.5 The role of chemotherapeutic agents is still controversial since scleroderma has been associated with various cancers. However, the onset of the disease in most patients appears to be in a closer temporal relationship with the administration of chemotherapy (mean period 16 months) than with the onset of neoplasia (mean period 42 months). Furthermore, the underlying cancer was in remission in most of patients, making a paraneoplastic nature of scleroderma unlikely. From this point of view, immune modulating activities of chemotherapeutic drugs may be responsible, together with their direct chemical effect, for triggering the immune cascade that activates fibroblasts.

An ischemic damage has been postulated for ergot derivatives and pentazocine.5 Vitamin K1 and vitamin B12 may induce morphea-like lesions locally, possibly in relation to a toxic effect of the vehicle or the preservative, or to a hypersensitivity reaction.75-77

Balicatib is a selective cathepsin K inhibitor, but some studies have showed that it can also inhibit cathepsins B, L and S, which are all expressed by skin fibroblast.5 Cathepsin K is a key enzyme in osteoclastic bone resorption. At the same time, it is able to degrade type I and type III collagen as well as elastin. It is plausible that the observed skin fibrosis in the described patients was a result of the inhibition of matrix-degrading functions of cathepsins in the skin.91

Finally, anti TNF-α seems to be implicated in rare cases of morphea.68 As a consequence of TNF-α suppression, TNF blockers may act on tumour growth factor beta 1 (TGF-β1), a pro-fibrotic cytokine involved in skin thickening, inducing an accumulation of the extracellular matrix through its actions on fibroblasts and endothelial cells.70 Another study points out the role of Th2 cells in the regulation of fibrosis reducing type I collagen synthesis by dermal fibroblasts. TNF-α, inhibition may dysregulate the balance between pro-fibrotic and anti-fibrotic triggers, promoting collagen deposition.

Conclusions

Our review was limited by the small number of cases reported. Not all the information regarding each patient were uniform. Moreover, for most of the cases described, only sporadic association with an offending drug was found. No clinical or histological differences among DI- DM or DI-morphea/SSc and the idiopathic counterpart were found either.

Thus, no uniform diagnostic criteria have been developed until now. Clinical improvement after withdrawal of the drug seems to be the only criterion that can help us in making diagnosis. Furthermore, an additional treatment was often necessary to control the disease.

In conclusion, DI- DM and DI-morphea/SSc seem to be rare. The patients must be monitored to exclude underlying diseases, such as neoplasms or autoimmune diseases. If the clinical possibility of a DI syndrome is encountered, drug discontinuation is recommended. Improvement of the lesions would support a pathogenic role for the guilty drug.

References

45. Fiorentino DF. Type I interferon in the induction or exacerbation of dermatomyositis: what this observation tells us about the naturally occurring disease. Arch Dermatol 2008;144:1379-82.
**Aim.** The use of skin needling is believed to aid the transdermal delivery of drugs, even if it is mostly used for skin collagen induction. The aim of this paper was to use skin needling, combined with a local anesthetic EMLA (eutectic mixture of lidocaine and prilocaine), as a way to enhance transdermal drug penetration and optimize the analgesic effects of common local anesthesia.

**Methods.** We recruited 15 patients. For each patient of our study we defined a skin area of $3 \text{ cm}^2$ from two forearms: on one side, we used skin needling first and immediately thereafter applied the EMLA in occlusion for 60 minutes; on the other, we only applied EMLA in occlusion for 60 minutes. Then, pain was induced in each patient’s forearm by introducing a 27 G needle into the skin 4 mm deep three times. Lastly, pain sensation measures were registered and a middle value was calculated.

**Results.** When skin needling is used in conjunction with EMLA applied in occlusion for 60 minutes on skin forearms, the level of pain sensation registered was significantly reduced on a Visual Analogue Scale compared to the application of EMLA alone.

**Conclusion.** The use of skin needling can improve the transdermal delivery of an emulsion-like eutectic mixture of local anesthetics (EMLA) and can introduce the use of this method for delivering topical molecules in dermatology.

**Key words:** EMLA - Anesthesia, local - Dermatology.

The stratum corneum (SC), the outermost layer of the skin, is the main barrier for transdermal drug delivery.\(^1\)\(^,\)\(^2\) This thin stratum ranges from 10 to 20 μm and can be considered a highly differentiated structure that controls the diffusion of compounds across the skin. The transdermal delivery of drugs is significantly restricted for the presence of the stratum corneum. To penetrate into the skin, drug molecule must be of small size and/or low molecular weight. Lipophilic molecules, which can carry a low therapeutic dose, can penetrate the skin deeper than hydrophilic ones.\(^3\)\(^-\)\(^5\) In the last few years transdermal delivery of active substances has become an important therapy used to treat a large number of skin diseases.

Skin penetration enhancement can be achieved either physically or chemically.\(^6\)\(^-\)\(^9\) Many techniques have been developed to improve transdermal drug delivery, such as electroporation,\(^10\)\(^,\)\(^11\) sonophoresis\(^12\)\(^,\)\(^13\) and iontophoresis.\(^14\)\(^,\)\(^15\) These techniques have shown to improve the permeability of the stratum corneum layer and enhance penetration of topical agents across the skin.

Recently the use of microneedles has been proposed as another strategy to dramatically increase drug delivery through the skin. Several authors have used microneedle injections with topical application to investigate if microneedles enhance in-vivo drug delivery through the stratum corneum: microneedle-injected sites showed a significantly higher transdermal penetration.\(^16\)\(^-\)\(^23\) Microneedles are also of most interest because they could offer painless drug delivery due to the absence of nerves in the
skin’s stratum corneum. In current practice, there is no evidence of microneedles penetrating 10-20 \(\mu m\) across the stratum corneum without entering the viable epidermis, where nerves are found. Instead, microneedles are inserted into the epidermis and sometimes into the superficial dermis. Nevertheless, microneedles are still reported as painless, probably because their small size reduces the odds of encountering a nerve or of stimulating it to produce a painful sensation.24

EMLA cream, an eutectic mixture of local anesthetics with lidocaine 2.5% and prilocaine 2.5% has been shown to decrease the discomfort of such procedures, particularly in pediatric patients. Although it is considered to be effective, its penetration is low and the onset of anesthesia is slow. Topical anesthesia for more invasive procedures such as split-thickness skin graft harvesting may require 1 to 2 hours EMLA application. This delay in onset of topical anesthesia is generally considered problematic.

**Procedure**

EMLA Cream (lidocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil element is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. It is used as a local skin anesthetic and applied to the skin before superficial surgical procedures or prior to the insertion of intravenous needles. For each patient of our study we defined a skin area of 3 cm\(^2\) from two forearms: on one side, we used skin needling first and immediately thereafter applied the EMLA in occlusion for 60 minutes; on the other one, we only applied EMLA in occlusion for 60 minutes (Figures 1-3). Then, pain was induced in each patient’s forearm by introducing a 27 G needle into the skin 4 mm deep three times. Lastly, pain sensation measures were registered and a middle value was calculated.

For the microneedling we used a skin needling tool (Dermaroller™ - Model CIT 8) that consists of a 12 cm plastic handle at the end of which lies a cylinder, like a small paint-roller, of 20 mm diameter and 20 mm length. On the surface of the cylinder are 24 circular arrays of 8 needles each (total 192 needles), with a needle length of only 0.05±0.02 mm and a diameter of 0.02 mm. Needles and disks are firmly bound together with a special medically approved adhesive.

Needles create microtrauma, microinflammation and very little damage in the epidermis and in the deep dermis. The healing phase is short: the skin appears mildly redness and swollen only for 24-48 hours. No side effects were observed.

**Objective**

The purpose of our study was to evaluate the use of microneedles in order to improve the transdermal delivery of EMLA used for superficial anesthesia in skin surgical procedures.

**Patients**

Fifteen patients were recruited for this study from relatives of in-patients of the Dermatology Division-University of Naples Federico II from patients who have to receive an excision treatment. All patients enrolled into the study gave an informed consent to partake in the study. The participants were recruited between October and December of 2011 and the sample was stratified by sex (10 females and 5 males) and by age (between 18 and 45 years, with an average of 23 years). Exclusion criteria included: patient refusal, contraindication to EMLA (allergy to any of its components, congenital methemoglobinemia, porphyria), concomitant use of an analgesic within the previous 24 hours, diabetes, neurologic sensorimotor disorders, infection localized to the site of puncture, damaged skin at the designated site, psychiatric disorder and dementia. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee.

**Pain evaluation grading**

The evaluation of pain sensation, an indirect expression of EMLA penetration, was performed by using a Visual Analogue Scale (VAS) (Figure 3). The level of personal pain experienced can only be indirectly measured by self-reported ratings, often by using a one-dimensional pain rating scale.25, 26 According to this measurement scale, the levels of pain ranges across a continuum from “none” to “worst” possible pain. Operationally a VAS is usually a horizontal line, 100 mm in length, with 0 on one end, representing no pain, and 10 on the other, representing the worst pain ever experienced. Patients mark on the line the point that they feel represents their perception of pain. The VAS score is determined by measuring in millimeters from the
Discussion and conclusion

EMLA cream, an eutectic mixture of local anesthetics with lidocaine 2.5% and prilocaine 2.5% has been shown to decrease the discomfort of such procedures, particularly in pediatric patients. Although it is considered to be effective, the onset of anesthesia is slow. The depth of penetration and degree of topical anesthesia attained following EMLA application depends on the duration of the application. McCafferty et al. have shown that following a 60 minutes EMLA application to the skin, only 45% of the subjects demonstrated complete loss of pin prick sensation at the site.28 Topical anesthesia for more invasive procedures such as split-thickness skin graft harvesting may require up to 2 hours EMLA application. This delay in onset of topical anesthesia is
inhconvenient as well as impractical in some clinical settings.\textsuperscript{29}

Recent reports have tried to identify the mechanisms involved in the enhancement of transdermal drug delivery and several hypotheses have been proposed, though none is completely exhausted.

To understand the mechanism by which microneedles increase skin permeability, McAllister \textit{et al.} theoretically modeled transdermal transport as diffusion through holes of known geometry made by insertion of microneedles. All scientific data is based on a repetitive rolling, of 10 to 15 times, on the same area of the skin.\textsuperscript{30} Kalluri \textit{et al.} have investigated the pore closure kinetics for the microchannels created by these stainless steel microneedles. The time taken for skin to restore its barrier function and to complete pore closure was investigated by calcein imaging studies. Calcein dye binds only living cells which are exposed upon disruption of the skin barrier, thereby indicating presence or absence of pores. In skin sites treated with microneedles, complete pore closure occur 12-18 h after poration, depending on the length of microneedles. Traditionally, chemical agents such as esters, azones, cyclodextrins, etc. have been employed in formulations as a means to alter the barrier properties of the stratum corneum layer of skin and aid in better permeation of the active agent. These permeation enhancers tend to disrupt the lipid structure of the SC layer, thereby causing damage which takes a long recovery time. The reversible nature of microchannels is very advantageous for controlled delivery of cosmetic agents/therapeutic compounds.\textsuperscript{31, 32}

The results of our study confirm the findings from previous reports and show that microneedles can be a useful approach in enhancing skin permeability and transdermal drug delivery. The potential advantages of this procedure include the significantly increased accumulation of a skin drug depot, short delivery lag times, simplicity and better penetration. Our study represents an interesting tool for further in-depth research and additional experimentation on the use of skin needling as a procedure improving the transdermal delivery of drugs.

\textbf{References}

SKIN NEEDLING FOR LOCAL ANESTHETICS DELIVERY


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Pyoderma gangrenosum (PG) is a rare, chronic neutrophilic dermatosis of unknown etiology. The worldwide incidence is estimated to be around 3-10 cases per million population per year. In 50-70% of cases inflammatory bowel diseases, hematological malignancies or rheumatologic disorders are associated to PG. Although the etiology is uncertain, the dysregulation of the immune system appears to be implied. Pathergy is the most important triggering factor of PG. Indeed, 20-30% of patients report the onset of PG following trivial trauma. Four main variants of PG have been described, namely classic, pustular, bullous, and vegetative forms. The classic form of PG is characterized by ulcers with a raised, undermined, inflammatory border. Intense pain is generally associated to PG. The diagnosis is mainly clinical and of exclusion. The differential diagnosis should take into account infections, vascular disorders and malignancies. The clinical course can be explosive and rapidly progressive or indolent and gradually progressive. Often patients develop only one episode and the overall prognosis is good but extremely influenced by the underlying disorders. Local therapy, mainly with topical steroids is used for mild to moderate lesions. For severe forms of PG a systemic therapy with glucocorticoids and/or other drugs such as tacrolimus, ciclosporine, etc. is needed. This paper is a systematic review of literature on PG.

**Key words:** Pyoderma gangrenosum - Inflammatory bowel diseases - Therapeutics.

Pyoderma gangrenosum (PG) is a rare, chronic neutrophilic dermatosis of unknown etiology, characterized by extremely painful nodules and pustules, which evolve into ulcers with a raised, tender and undermined border. The cutaneous lesions might be the only manifestation of the disease, but in 50-70% of cases, PG is associated to a systemic disease, such as: inflammatory bowel diseases (IBD), hematological malignancies and rheumatologic disorders. Furthermore, pyodermic lesions are typically triggered by pathergy, which is reported in 30% of patients.1

**Epidemiology**

The first description of PG was given by Brocq in 1916, naming this condition “phagédénisme géométrique”.2 However, it was thoroughly described for the first time as a nosographic entity in 1930 by Burnsting et al., at the Department of Dermatology of the Mayo Clinic.3 The authors coined the term pyoderma gangrenosum and hypothesized a possible infectious etiology.

The worldwide incidence of PG is uncertain, but it is approximately estimated to be around 3-10 cases per million population per year.4 While, according to other authors, the incidence of PG is about 1 case per 100,000 population per year.5, 6

PG occurs at any age, but the peak of incidence is between the ages of 20-50 years.1, 7 Only 3-4% of cases of PG occur during childhood or adolescence and it’s only occasionally described in elderly people.8 Females tend to be slightly more affected than men.
Etiology and pathogenesis

The etiology and pathogenesis of PG are not yet completely understood. In the 1980s, Fulbright et al. had already advanced the hypothesis, that an aberrant immunological response to undefined factors could be responsible for the clinical manifestations of PG. Indeed, systemic diseases, characterized by immunological alterations, are often associated with PG. Furthermore, an exaggerated inflammatory response to non-specific stimuli characterizes the pathergy phenomenon, which consists in the onset of new lesions or the worsening of the existing ones following minimal trauma. These elements suggest that the dysregulation of the immune system is probably implied in the pathogenesis of the cutaneous lesions.

Since IBD are frequently associated to PG, Van den Driesche et al. hypothesized the possible cross-reactivity between intestinal and cutaneous antigens, which could explain the genesis of the cutaneous lesions as manifestations of the underlying disease.

Other elements that support the immunological pathogenesis are the ex adjuvantis criteria. Indeed, lesions heal with immunosuppressant drugs and anti-TNF-α biologics. Always according to this criterion, a T-cell response was hypothesized, based on the efficacy of T-cell inhibiting drugs and T-cell apoptosis inducing agents.

Chemotactic defects and hyperactivity of neutrophils might play a role in pathogenesis. In particular, abnormal neutrophil trafficking, metabolic oscillations, aberrant integrins, and insufficient cutaneous protection from neutrophilic infiltration were described.

IgA gammopathies have been demonstrated to alter in vitro the chemotaxis of neutrophils, setting the basis to hypothesize that IgA might influence the function of neutrophils in vivo as well. Furthermore, PG is associated in 10% of patients to monoclonal or polyclonal hypergammaglobulinemia, especially IgA and less often IgG or IgM.

Various studies demonstrated an over-expression in skin biopsies taken from pyodermic ulcers of IL-8, a powerful chemotactic factor for neutrophils. Oka et al. obtained ulcers absolutely similar to the pyodermic ones, on human skin xenografts, transplanted on immunodeficient mice, infected by a recombinant virus, able to induce an IL-8 over-expression in human fibroblasts. These clinical data and experimental results suggest that IL-8 might play an important role in pathogenesis of PG.

The deposition of proteins in the walls of cutaneous vessels in PG, has suggested a possible vasculitic etiology, due to a type III hypersensitivity reaction. Indeed, the direct immunoflorescence reveals IgM, C3 and fibrin deposits in vessels of the reticular and papillary derma in 55% of cases. Less frequently IgA and IgG deposits are detectable. Furthermore, Su et al. demonstrated a characteristic morphological and pathological evolution of the lesions on biopsy specimens obtained from the necrotic border of the ulcer. The initial lesions present a mild to moderate perivascular infiltration of lymphocytes and endothelium edema. The completely developed lesions show necrosis, a dense perivascular infiltration, extravasated erythrocytes and thrombosis. While ulceration, infarction and abscesses are visible only in later phases. The evolution of the lesions suggests that the initial damage might have a vasculitic origin.

Certainly the most important triggering factor is pathergy (Koebner phenomenon), reported in 20-30% of patients affected by PG. Any kind of skin trauma, due to surgery, injections, prick tests, insects bites can induce a new lesion or worsen the preexisting ones. Interestingly sometimes patients refer (especially in the USA) a spider bite, especially by brown recluse spiders (Loxosceles reclusa). Although, it’s uncertain whether the venom of the spider is only a triggering factor or if it is sufficient to determine the lesion itself.

Durg-induced PG has been reported in literature and the implied drugs are: propylthiouracil potassium iodide, pegfilgastrim (granulocyte macrophage colony-stimulating factor) and gefitinib (epidermal growth factor receptor inhibitor).

Clinical features

Powell et al. classified PG into four major clinical variants: ulcerative, pustular, bullous and vegetative. The most frequent one is the ulcerative type, also known as classic form. Generally one clinical form predominates on the others, but sometimes different types might coexist in the same patient.

Classic form

This form is characterized by an ulcer with a raised inflammatory border and a wet necrotic base (Figure 1).

The primary lesion starts as a painful nodule or
These atypical lesions resemble the purplish plaques found in Sweet’s syndrome, making the differential diagnosis quite difficult between these two diseases. Since this type of PG is frequently associated to underlying hematological disorders (i.e. myeloid leukemia and myeloproliferative disorders), the work up to rule out a possible underlying malignancy should always be done in these patients. Bullous PG often has a poor prognosis due to the underlying neoplasia. Koester *et al.* have reported a mortality rate of 82.6%, with death occurring on the average 7 months after the diagnosis. Moreover, they hypothesized that a possible neutrophilic infiltration of the inner organs could be the cause of the elevated mortality rate.

**Pustular form**

It’s a rare variant of PG, described for the first time by O’Loughlin and Perry in patients with active IBD. Indeed, this form is almost exclusively associated to IBD. It’s a *forme fruste* of PG, since the lesions stop at the pustular phase, without evolving into ulcers. The clinical presentation is characterized by multiple sterile pustules, surrounded by an erythematous halo, with possible systemic symptoms such as fever, arthralgias and myalgias. The lesions localize, often symmetrically, on the extensor surfaces of the limbs and on the trunk. The pustular eruption can regress by treating the underlying condition.

**Atypical or bullous form**

Bullous PG is a superficial variant of PG that mainly regards the face and the upper limbs (especially the back of the hands). This form of PG is frequently associated with hematological malignancies and it was described for the first time by Perry and Winkelmann in 1972. The lesion is characterized by hemorrhagic blisters or plaques in concentric expansion, that might break causing an ulcer, usually much more superficial than the classic pyodermic lesions, but still presenting an undermined border.

**Vegetative form**

The vegetative form is a superficial, more localized and less aggressive variant of PG. It also responds better than other forms to local treatment. Perry *et al.* initially considered it as a separate entity, defining it malignan pyoderma; while Gibson *et al.* have more recently classified it as an atypical manifestation of Wegener’s granulomatosis. The lesions are verrucous and shallow ulcers, without the typical undermined border and erythematous halo. The most frequently affected areas are the head and neck.
Other penile PG in a HIV positive patient described by Ecra et al. The differential diagnosis should be performed between PG and sexually transmitted diseases and Behçet’s disease.

Extracutaneous PG

The extracutaneous localizations rarely complicate PG. The lesions are sterile abscesses, in which no pathogens can be detected. Lungs are the most commonly involved extracutaneous site, however sterile infiltrates have been described in the heart, skeletal muscles, bones, central nervous system, spleen, liver, lymphonodes, gastrointestinal tract and cornea. The bone lesions are commonly defined as recurrent sterile multifocal osteomyelitis.

Peristomal PG

This condition occurs around abdominal stomas and comprises about 15% of all cases of PG. Almost all of these patients are affected by IBD, especially Crohn’s disease, and underwent surgery for the placement of an ileostomy or a colostomy. However, some cases have been described following a ileo- or colostomy performed because of intestinal malignancies, diverticular disease or after an urinary diversion following a radical cystectomy.
Based on a large study, peristomal PG occurs in about 0.6% of patients with abdominal stomas. Generally the lesions appear from 2 months to 25 years after the enterostomy. The continuous trauma of the skin surrounding the stoma, the irritation caused by fecal loss and the stoma bag adhering to the abdominal wall may evoke the pathergy phenomenon and trigger new lesions. Furthermore, a vicious cycle might begin: the lesion can reduce the adherence of the stoma-bag to the peristomal skin, so more irritating fecal material might spill out, worsening the wound even more. Surgical debridement, grafting or replacing of the stoma might as well induce new lesions. Commonly the peristomal PG is mistaken for a surgical site infection, therefore a precise differential diagnosis is vital, in order to start as quickly as possible the steroid therapy and to guarantee the healing of the wound, as a Japanese study demonstrates.

**PG and surgery**

In literature PG is also reported to be a complication of different kinds of surgery, probably due to the pathergy phenomenon. It is often described as a complication of additive or reductive mastoplasty and to a lesser extent of other types of surgery such as hernioplasty, heart-surgery, and head and neck surgery. Wollina advanced the hypothesis that the areas with thicker subcutaneous fat tissue, are the ones with a higher risk of developing PG as a complication of surgery; this would explain why mastoplasty is so frequently involved. In international literature only 400 cases of PG of the breast can be found, most of which following breast surgery. As the peristomal forms also these forms of PG are often initially misdiagnosed, since they are mistaken for surgical site infections. However, it is extremely important to recognize it promptly in order to avoid surgical debridement, which would only worsen the lesion, and to start a steroid therapy. As in the other cases of PG, these patients generally have underlying systemic diseases and surgery is only the triggering factor for the skin lesion.

If patients with a history of PG must undergo surgery, excessive skin trauma should be avoided, surgery should be as fast as possible, the surgical wound should be kept as small as possible, suturing ought to be performed carefully and all in all prophylactic systemic perioperative steroids or cyclosporine are recommended.

**Associated diseases**

Fifty-seventy percent of cases of PG are associated with an underlying systemic condition; most frequently IBD (30%), arthritis (25%) and lymphoproliferative disorders (10%) (i.e. myeloid leukemia, hairy cell leukemia, myelofibrosis and monoclonal gammopathy).

After erythema nodosum, PG is the second most common extraintestinal manifestation of IBD. PG is reported in 2-12% of patients with IBD and the 30% of all cases of PG are associated to an underlying IBD, of which 10-15% are attributable to ulcerative colitis and a similar amount to Crohn’s disease. The lesions of PG generally appear after the clinical onset of ulcerative colitis, however a few cases were reported in which the cutaneous lesions would precede the bowel disease or even occur after the removal of the affected intestinal tract. In most patients intestinal flares go hand in hand with the worsening of the cutaneous lesions, but in many other cases there is no correlation between the clinical course of the two conditions. Sometimes, PG persists during the quiescent phases of the ulcerative colitis. PG has also been described in association to Crohn’s disease, but to a lesser extent. The ulcerative and pustular form are most frequently associated forms to IBD. Furthermore, PG-like lesions are reported in the aseptic abscesses syndrome, a new entity within the spectrum of Neutrophilic Dermatoses which frequently occurs in association with IBD and is characterized by deep abscesses mainly involving the spleen and skin and by polymorphic cutaneous manifestations.

PG is sometimes associated with: classical seropositive arthritis, seronegative rheumatoid-like arthritis, Felty’s syndrome, osteoarthritis, and sacroiliitis. In other patients PG is associated to IBD related arthritis: seronegative, acute, oligoarticular, and non-destructive arthritis and spondylitis.

Other particular associations with SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) and with psoriatic arthritis have been described. The rheumatological manifestations generally precede the cutaneous lesions.

High titers of IgA and less frequently IgG and IgM are found up to 15% of patients with PG. Even though most of patients with paraproteinemia over short-term don’t show a progression to malignancy, some patient already have myeloma at the diagnosis or develop it afterwards. Myeloma usually appears
Inflammosomes are molecular platforms responsible for the activation of the caspase 1, a protease cleaving the pro-interleukin-1 to functionally active IL-1-beta. The overproduction of IL-1-beta triggers the release of more pro-inflammatory cytokines and chemokines, inducing the recruitment and activation of neutrophils and leading to a neutrophil-mediated inflammation which is the pathophysiological hallmark of the neutrophilic dermatoses.

**PG and pregnancy**

PG is extremely rare during pregnancy and puerperium. Less than 20 cases are reported in international literature, although pregnancy, according to Wollina et al., might be a triggering factor for neutrophilic dermatosis, due to high G-CSF levels and pathergy.

**PG and childhood**

It is a rare form of PG, since only 3-4% of all cases of PG occur during childhood. The skin lesions in children have overall a similar aspect and localization to the ones reported in adults, but especially in newborns the genital and perianal regions might be involved. The correlated systemic disorders are the same as those described in adults: 40% of children with PG are affected by IBD, 18% by leukemia and occasionally by AIDS. Most of the time children have a favorable prognosis.

**Histopathology**

There is no specific histopathological hallmark for PG, therefore the diagnosis is mostly clinical. However, a skin biopsy should always be performed, in order to rule out other possible causes of ulceration (malignancies and vasculitides). The histological presentation changes according to evolutionary stages of the lesion and to the site of the biopsy. In early lesions and in biopsies taken from the erythematous halo, the inflammation tends to be confined to the dermis and causes vasculitic-like lesions in blood vessels, in which a lymphocytic infiltration predominates and fibrinoid necrosis in the walls of vessels is visible. Occasionally thrombosis and extravasation of red blood cells are detectable.

In the later phases and in biopsies taken from the border closer to the center of ulcer, neutrophilic inflаr-
Even though there are no specific histological characteristics of PG and despite the risk to determine the enlargement of the ulcer, a biopsy of lesional skin should always be performed. In the biopsy protocol, suggested by Weenig et al., an elliptical incision is preferable to a punch biopsy in order to include subcutaneous fat in the biopsy specimen. On specimen from the erythematous halo routine hematoxylin and eosin staining and special staining for microorganisms (Gram’s, methenamine silver and Fite) should be performed; while with the material taken from the center of the ulcers cultures in appropriate media to detect bacteria, fungi and atypical mycobacteria must be performed. Laboratory investigations should include complete blood count, erythrocyte sedimentation rate, blood chemistry (liver and kidney function), and coagulation panel (including antiphospholipid-antibody screening). A full blood workup will probably show high inflammatory indices and leucocytosis. At times sideropenic anemia and hyperglobulinemia might be reported. No pathognomonic auto-antibodies are titrable for PG. Circulating immune complexes are not detectable and complement fractions are not consumed. As well as no significant HLA-association has been demonstrated. Further exams should comprise: ANA, ANCA, rheumatoid factor and cryoglobulin titration.

Gastrointestinal evaluation should always be considered in patients with PG. The gold standard exam in order to assess IBD is a colonoscopy with biopsies for the histological confirmation.

If hematological malignancies are suspected, in addition to a complete blood count, peripheral blood smear, bone marrow aspiration and biopsy might be useful. While blood and urinary protein electrophoresis can identify monoclonal gammopathies or a myeloma.

A chest X-ray is necessary to exclude pulmonary infections or systemic vasculitides with lung involvement. Ultrasounds or an angiography should be performed, if circulation issues are suspected in lower extremities.

Su et al. proposed diagnostic criteria for classic PG, might be useful in clinical practice, even though they are not universally accepted. The following are Su et al.’s criteria revised by Callen et al.
Major criteria:
— rapid progression (margin’s expansion 1-2 cm/day or a 50% increase of ulcer size in 1 month) of a painful (pain is generally out of proportion to the size of the ulceration); necrotic ulcer with an irregular, violaceous, and undermined border;
— exclusion of other causes of cutaneous ulceration.

Minor criteria:
— history suggestive of pathergy or clinical finding of cribriform scarring;
— systemic diseases associated with PG;
— histopathologic findings (sterile dermal neutrophilia ± mixed inflammation ± lymphocytic vasculitis);
— treatment response (rapid response to systemic glucocorticoid treatment) (generally responds to a dosage of 1-2 mg/kg/day, with a decrease in size within 1 month).

Differential diagnosis

The differential diagnosis can be rather complex, due to the wide variety of possible causes of cutaneous ulceration. Dabade et al. report that in the Mayo Clinic case series, 10% of patients diagnosed with PG, were actually misdiagnosed. The same authors underline the importance of a correct diagnosis in patients with unusual ulcerations. On the one hand not recognizing a PG means the relentless enlargement of the lesion, while a correct diagnosis and a prompt therapy can rapidly heal the wound. On the other hand over diagnosing PG entails an inappropriate use of immunosuppressive drugs with relative side effects and since the treatment is not effective the patient might be exposed to further risks, especially if the real cause is infectious. The differential diagnosis is mainly clinical and all of the other possible causes of ulcerative and erosive skin lesions, including above all infections, vascular disorders and malignancies should be considered.

Infectious disease that resemble PG are:
— bacterial infections: pyogenic infections such as erysipelas, cellulitis, necrotizing fasciitis, erythema gangrenosum; systemic infections by Pseudomonas aeruginosa and syphilitic gummas;
— viral infections: herpetic (HSV) ulcers;
— mycobacterial infections: including cutaneous tuberculosis, Buruli ulcer (caused by Mycobacterium ulcerans) and atypical mycobacterial infections;
— parasitic infections: cutaneous leshmaniosis and amoebiasis;
— fungal infections: deep infections mainly sporotrichosis but also blastomycosis, cryptococcosis, coccidioidomycosis, histoplasmosis and aspergillosis.

In order to out rule infections, cultures from swabs, exudation or biopsies should be performed. Cultures should be kept at least for six weeks, since some microorganisms might have slow growth rates.

The vascular disorders, both venous and arterial, are a major cause of cutaneous ulceration and must be appropriately excluded.

Some types of systemic vasculitis, such as polyarteritis nodosa, mixed cryoglobulinemia (generally associated with hepatitis C) and ANCA (antineutrophil cytoplasmic antibodies) associated vasculitides, might cause ulcerative lesions similar to the ones seen in PG.

Veno-occlusive disease should be ruled out by evaluating all of the risk factors for such disease. In particular, a few thrombophilic conditions might be mistaken for PG, such as livedo reticularis, antiphospholipid syndrome, factor V Leiden mutation, methyl-tetrahydrofolate-reductase polymorphism, protein C and protein S mutations and antithrombin III deficiency.

Other than the veno-occlusive disorders, peripheral arterial occlusive disease should be always be taken in consideration. Within this context atherosclerotic and traumatic arteropathy and cholesterol microembolization syndrome should be kept in mind.

Malignancies that can emulate PG include: squamous-cell carcinoma, cutaneous lymphoma, leukemia cutis, metastasis of carcinoma, melanoma, Kaposi sarcoma and angiosarcoma.

A very difficult differential diagnosis should be made between PG and self induced skin lesions, which are also diagnosed by using exclusion criteria. Histopathology is completely nonspecific and the injected or applied substances (urine, disinfectants, detergents) are not identifiable. Perfectly straight lines and lesions forming acute angles, should alert the clinician, for it might be a self induced lesion. Since diabetic ulcerations are quite common, they should always be taken in account in the differential diagnosis of PG.

Moreover, autoimmune disorders, which can result in cutaneous lesions, such as bullous diseases and connectivitis including lupus erythematosus,
polyartheritis nodosa and Wegener’s granulomatosis must be ruled out. Extremely relevant is the differential diagnosis with Sweet’s syndrome, another neutrophilic dermatosis, characterized by sudden onset of fever and a papulo erythematous eruption.

Patients affected by Crohn’s disease might present non-caseous granulomas typically localized at the upper limbs as a rare cutaneous metastatic complication of the underlying disorder. These manifestations ought not be mistaken for PG.

Insects bites, especially spider bites, might lead to necrotizing lesions; this hypothesis should be carefully considered if the lesions are on an extremity. However, in spider bites, the expansion of the lesion is faster and is commonly associated with systemic symptoms (e.g. disseminated intravascular coagulation).

**Course and prognosis**

The clinical course can follow two different patterns:

1) explosive onset with fast progression, clinically characterized by fever, toxicity, pain, hemorrhagic pustules, wide areas of necrosis and an intensely inflammatory halo;

2) indolent and gradually progressive: granulation tissue at the base of the ulcer, crusts and hyperkeratosis of the margin are clinically seen. The growth of the ulcer is slow over months and it regards broad skin areas and it is characterized by resolution in one spot and progression to another.

In both cases there can be a spontaneous resolution of the lesions, resulting in an atrophic, cribriform and hypopigmented scar. A promptly made diagnosis can avoid disfiguring scarring. An objective evaluation of the ulcer, done by measuring its depth, width and length, as well as sequential photography represent excellent parameters for the assessment of the evolution of the ulcer in time and of the efficacy of therapy. The extent of the inflammatory component is evaluated by the dimensions of the erythema and by expansion of the ulcer. In fact, when the border flattens and the erythema reduces therapy can be gradually reduced.

Many patients with PG develop only one isolated episode, that resolves with a short course therapy, with no other relapse. Some times after the first episode, the disease remains silent for months or even for years, but then it may relapse after trivial trauma, surgery or without any clear triggering factor. Moreover, other patients have a chronic relapsing course, which requires a long term therapy. In spite of the progress made in therapy, the long term outcome for patients with PG remains uncertain. PG is a potentially mortal disease, with a mortality rate that reaches 30% in a few case series. Poor prognostic factors are: male gender, onset in old age and the bullous form of PG, especially if it’s associated to underlying hematological malignancies.

The prognosis is more easily predictable in those patient with a systemic underlying disorder, that can be identified and cured. Although, even in these cases prognosis might be poor according to the type of systemic disease, especially if the immune system is involved.

If PG is associated to IBD, the clinical course of both diseases can be parallel and the regression of the cutaneous lesions is possible by treating the enteropathy. However, the skin ulcers might have a completely different and independent course compared to the activity of IBD. Even if some Authors have suggested the correlation between the cutaneous onset and the flares of IBD, others didn’t report this relationship.

A quick response to treatment suggests a good course of PG.

**Management and therapy**

Probably because PG is a very rare, only a few clinical trials were made on the treatment of this pathology. There is no gold standard therapy for PG. Since the pathogenesis is not perfectly known, the therapeutic approach is mostly empirical and there is no specific and constantly effective therapy. The therapy is chosen based on multiple factors, including the extension and depth of the ulcer, the associated systemic diseases and the patient’s performance status. Other elements that influence the therapeutic choice are the side effects of drugs, since in more than 50% of cases of classic PG long term-therapy is required in order to obtain and maintain a long-lasting remission. The goals of therapy are: turn off inflammation, reduce pain and to control the underlying disorder.
Local therapy

The local treatment requires cleaning and avoiding bacterial over-infections. However, a more invasive surgical debridement is always discouraged, in order not to induce a further extension of the ulcer, due to the pathergy phenomenon.

Topical therapy is the first choice treatment for mild to moderate lesions in early stages (papules, pustules, nodules or superficial ulcers) and includes dressings, topical agents and intraleseional injections. Topical agents might be useful as additional treatment to the systemic therapy in more severe forms of PG. Many topical agents were demonstrated to be effective in small studies, however, no large trials have confirmed it.

The most commonly used topical agents are potent, super-potent steroids and tacrolimus. Tacrolimus is particularly effective on peristomal PG, in monotherapy or associated with other drugs. Systemic absorption of topical agents is possible and its entity should be controlled. Indeed, a few cases were reported of patients, who by daily applying topical tacrolimus, reached high blood levels of this drug, resulting in a systemic immunosuppressant effect. Anyhow, this side effect is very rare (only two cases were reported in literature) and there were no severe consequences for the patients. As Schadt and Callen suggested this event might be related to the extent of the treated area and to the severity of the ulceration.

In some patients 5-aminosalicylic acid, pimecrolimus 1% (associated with prednisone), nicotine, cromoglycate sodium, nitrogen mustards and benzoyl peroxide were proven effective. In other patients, with healing lesions but with slow re-epithelization the topical use of platelet-derived growth factor was helpful. Other treatment options are intralesional injections in the border of the ulcer twice a week of steroids, cyclosporine or triamcinolone acetonide (5 mg/mL), which was the most effective above all. Although, not all authors agree on using intralesional injections as first line therapy, because of the possible worsening of the lesion as a consequence of pathergy.

Even though the ulcer is not caused by infection, there might be a colonization by bacteria producing malodorous substances; in this case an antibiotic therapy with metronidazole can reduce the odor.

Autologous split-graft surgery gave variable outcomes. New developments were made in skin bioengineering, for example dermal regeneration template, hair follicle stem cell-derived autologous keratinocyte sheets or hyaluronic acid-based autologous keratinocyte delivery system were successfully used for the treatment of PG.

Systemic therapy

In patients with severe forms of PG in rapid expansion and resistant to topical treatment, a systemic therapy is needed. Glucocorticoids, tacrolimus, cyclosporine, dapsone, sulfapyridine, azathioprine, mycophenolate mofetil, methotrexate, chlorambucil, thalidomide, colchicine and cyclophosphamide are all possible options for the systemic therapy of PG.

Corticosteroids and cyclosporine are the first line drugs. Steroids are used in the acute phase of the disease and generally give predictable and tangible effects. The initial dose is generally quite high (100-200 mg/day of prednisone) that has to be reduced as the inflammation shuts down and then gradually suspended when the complete resolution occurs. In order to avoid excessive toxicity it is necessary to reduce the doses of steroids, by using steroid sparing drugs already in the initial phases, if the lesions therapy resistant.

Pulse therapy with high doses of methylprednisolone (1 g/day for five consecutive days) is the most effective treatment for severe, aggressive and rapidly expanding forms of PG.

Cyclosporine is another first line option in treating PG by inhibiting T-cells. Various retrospective studies and plenty case reports have demonstrated the efficacy of cyclosporine, however long term therapy might be problematic. Cyclosporine in monotherapy induces a rapid remission of the disease at a dose of 3-6 mg/kg/day after a few weeks of treatment and the complete resolution of the lesion after 1-3 months. Furthermore, cyclosporine was shown to be a valid steroid sparing agent for those patients with skin lesions resistant to steroid therapy and for those patients who present severe side effects of such a therapy. Some patients require low maintenance dose, while others can stop the treatment completely. Some patients might need an associated low dose steroid therapy. Not even cyclosporine is free.
from side effects in long term therapy, in particular it can induce hypertension, renal damage and secondary tumors.

Sulfur drugs, such as dapsone, sulfapyridine and sulfasalazine are used in systemic therapy as well. Ruocco et al. reported a higher efficacy of sulfasalazine both in patients with IBD and in patients without underlying disorders.\(^1\) The initial dose of sulfasalazine is in between 4-6 g/day, gradually reduce to 0.5-1 g/day. An association with steroids might be necessary especially in the early phases of the disease, but in spite of that some patients don’t respond to therapy. The dosage of dapsone can be brought up to 200 mg/day in monotherapy or associated to a steroid-sparing agent but generally the dose ranges from 100-150 mg/day. The evaluation of side effects of this therapy is very important, especially attention must be paid to the formation of methemoglobin.

The exact mechanism of action of sulfur drugs in PG is unknown, probably it induces the stabilization of lysosomes and interferes with the function of neutrophilic myeloperoxidase reducing the ROS production and reduces the viscosity of glycosaminoglycans.\(^1,10\)

Usually Clofazimine is very effective at the dosage of 200-300 mg/day, only in some patients the treatment is ineffective. An isolated case of splenic infarction was reported,\(^10\) and more frequently hyperpigmentation is seen. Clofazimine at higher doses (300-400 mg/day) is comparable to the efficacy of sulfur drugs.\(^8\)

Other used immunosuppressant agents are azathioprine, methotrexate and 6-mercaptopurine; although these drugs are not universally effective.

Azathioprine (100-150 mg/day) is a cytotoxic drug used as a steroid-sparing agent. Its action is tangible after 2-4 weeks. White blood cell count and transaminases need to be checked in patients undergoing such therapy.\(^8\) Metabolization rates for this drug are significantly different between individuals, because of the polymorphism of the thiopurine methyltransferase, an essential enzyme in the detoxification of azathioprine. Azathioprine and sulfasalazine are excellent choices in patients affected by Crohn’s disease or ulcerative colitis.\(^8\)

Cyclophosphamide is another cytotoxic agent that can induce remission in some patients, however severe side effects such as infertility, hair loss, secondary tumors, hemorrhagic cystitis, can derive from this therapy. Pulse therapy is practiced, alternating methotrexate or azathioprine in Crohn affected patients resistant to steroid therapy. With such a regime remissions for more than 30 months can be obtained.\(^8\)

Mycophenolate mofetil is an inhibitor of purinic synthesis, which reduces T-cell and B-cell proliferation. The dose of 2-4 g/day is used both in monotherapy or associated with topical or systemic agents is effective in a few cases and shows a better safety profile as far as renal function is concerned in long term therapy compared to steroids or cyclosporine, making this agent an excellent option in responsive patients.\(^74\) Very few cases were reported of sepsis by staphylococci or pseudomonas in patients undergoing this therapy.

Also chlorambucyl (4 mg/day) is a good steroid-sparing agent.

Anecdotal reports

Thalidomide has an immunomodulatory activity by inhibiting TNF-alfa, basic fibroblast growth factor (BFGF) and by reducing chemotaxis of neutrophils. This agent has been successfully used associated to steroid therapy.\(^94\)

Colchicine inhibits the mitotic bundle and has anti-inflammatory properties. Kontochristopoulos et al. report the only case in which this drug was used for the treatment of PG.\(^89\) Monotherapy or associations are possible and gastrointestinal side effects might limit its use.\(^8\)

Tacrolimus is a selective inhibitor of calcineurin, used as a systemic treatment at the dose of 0.1 mg/kg/day. During treatment serum levels of the drug should range from 4-6 ng/L.\(^8\) Lesions completely disappear in patients with underlying ulcerative colitis.

Due to the risks related to the immunosoppressive therapy, recently the intravenous immunoglobulin therapy (IVIG) was experimented. In a retrospective study out of 10 patients with classical PG, 7 showed complete resolution of the lesions by using IVIG 2 g/kg divided into 3 doses given in 3 consecutive days in one month. The side effects of IVIG include nausea, headache and a case of aseptic meningitis was reported. On the down side costs of this therapy are very high. Associating IVIG to intravenous thalidomide was proven useful in cases of PG associated to Bechter disease.\(^10\)
Biologics

Generally TNF-α inhibitors are chosen if patients are already affected by Crohn’s disease or rheumatoid arthritis. Endovenous infliximab is preferred to subcutaneous injections of etanercept or adalimumab, which could evoke pathology.21 It’s a third line therapy for patients who don’t respond either to steroids nor cyclosporine. Very recently Gisondi et al. underlined how monoclonal antibodies, infliximab and adalimumab were effective in improving quality of life (QoL) in patients with PG.95 Infliximab is the only biologic agent for which randomized, double blind with placebo studies are reported in literature, which means its efficacy is evidence based.95 The maintenance dose is still to be correctly determined. In various studies the whole dose was divided into 3 doses (0, 2 and 6 weeks) with a 5mg/kg infusion. This protocol allowed a dramatic cutaneous and intestinal improvement and as maintenance therapy azathioprine was used in order to reduce steroids and infliximab.96

In a few case series etanercept was used for PG. In most cases 50 mg/weekly were given in only one dose or two doses of 25 mg each. The results in all studies were of a dramatic reduction of the dimensions of the ulcer or even complete resolution.97 Adalimumab is another TNF-α inhibitor, used in 8 patients with PG up till now.98 Independently from the dose, most patients showed improvement or regression within 2 weeks or 2 months maximum. In most cases the biological agent was not permanently suspended, but was kept as maintenance therapy. Very few cases were reported of effective treatment with efalizumab (withdrawn in Italy), but Woodson et al. described a case of a patient non responding to any other therapy but responsive to this biologic after 6 weeks of treatment.99

Finally a recent study defined alefacept, a T-cell immunomodulator, as a valid treatment option in these patients.100 After 20 weeks of 15 mg/im/day out of 4 patients, one obtained a complete resolution, two showed dramatic improvement and the last one had a moderate improvement. After 32 weeks two patients were completely healed.

Therapeutic leukocytapheresis

The selective granulocyte/monocyte adsorption apheresis (GMA) was demonstrated to be an extremely effective therapeutic approach for patients with ulcerative colitis, as well as Behçet disease, psoriatic arthritis and other neutrophilic disorders, including PG.101 GMA is an extracorporeal leukocyte apheresis device, filled with specially designed cellulose acetate beads as adsorptive carriers. The adhesion of leukocytes to the cellulose acetate beads is mediated by the Fcγ receptor, hence the adsorption is specific for Fcγ receptor bearing cells, i.e. activated granulocytes and monocytes. Therefore GMA reduces the production of TNF-α and removes activated granulocytes and monocytes from peripheral blood. This non-pharmacological treatment has an excellent safety profile and patients with PG or psoriasis-like skin lesions are reported to be the best responders to such therapy.102 Ikeda et al.101 report a case of PG associated to IBD dramatically improved by this therapy. These Authors report a significant decrease of serum levels of IL-8 and G-CSF in such patient, suggesting the relevant role of these cytokines in the development of PG. While Hanai et al. underline that the response of PG lesions was more striking than anything expected from GMA. These authors also report that the CXCR3, a chemokine receptor know to have an important role in skin inflammation, was strongly down regulated by GMA.102

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PYODERMA GANGRENOSUM


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Spitz/Reed nevi: proposal of management recommendations by the Dermoscopy Study Group of the Italian Society of Dermatology (SIDeMaST)


Spitz nevus is a benign melanocytic neoplasm mostly appearing in the pediatric age and clinically consisting of a single, pink, red or brown papule, mainly observed on the face and limbs and characterized by an initially rapid growth.1-6 Reed nevus is the pigmented variant of Spitz nevus, which appears more frequently on lower limbs and has equally dynamic morpho-evolutive aspects.

Histopathologically, both Spitz and Reed nevi are typified by a proliferation of large epithelioid and/or spindle-like melanocytes.7, 8 Therefore, the 2 entities will hereafter be referred to under the “umbrella” term “Spitz/Reed nevus”.

The diagnosis of the most typical variants of Spitz/Reed nevus does not generally pose any problems of interpretation, especially in the pediatric age. On the other hand, the diagnosis of atypical forms is more complex, due to the morphologic overlap with atypical Spitz/Reed tumor and Spitzoid melanoma. The latter is particularly relevant for Spitz/Reed nevi arising in adults.

Recent advances in the histopathologic classification of Spitz/Reed nevi have improved the reliability of microscopic diagnosis, narrowing the interpretative “grey areas”. Furthermore, the gradually acquired experience in the use of dermoscopy and videodermoscopy along with data provided from longitudinal studies concerning the evolution of Spitz/Reed nevi.9-11 facilitated the more accurate...
diagnosis and appropriate management of pediatric Spitz/Reed nevi.12-14

By combining the existing evidence and our own experience, our purpose was to provide a comprehensive summary on the clinical and dermoscopic characteristics of Spitz/Reed nevi, aiming to allow clinicians better diagnosis and management of Spitzoid lesions.

A still open debate

Spitzoid lesions are generally characterized by an extremely dynamic clinical and dermoscopic evolution in the course of time. Their rapid morphologic alterations often force clinicians to excise the lesions in order to resolve their diagnostic uncertainty by histopathologic examination. The introduction of confocal microscopy may constitute a valuable and promising alternative to histopathologic examination, even if its use is still limited to a restricted number of Italian hospitals. Despite the improvement of histopathologic and immunohistochemical techniques and the experience that pathologists have acquired in evaluating Spitzoid lesions, the debate about the accurate classification of Spitzoid neoplasms is still open. In fact, several attempts to reach a consensus on the “grey areas” – constituted by Spitzoid lesions of more complex interpretation – has so far resulted in the suggestion of a “case by case” evaluation, integrating clinical and histopathologic information.

Spitzoid lesions represent an articulate complex of entities with different biologic behavior, with the completely benign Spitz/Reed nevus at the one edge and Spitzoid melanoma at the other, while the malignant potential of atypical Spitzoid lesions that lay in between is uncertain and controversial. This causes significant difficulties in their interpretation and results in a great heterogeneity of management strategies.

A recent paper15 has shown that 95.8% of American dermatologists consider Spitz/Reed nevus a benign entity and recommend classification follow up in about 50% of cases. However, the criteria warranting excision were not clearly discussed, not allowing the development of a management plan applicable in the clinical practice.

Our suggestions are based on existing evidence, as well as on the experience our research team has acquired over the years. Our aim was not to thoroughly review the controversial topic of histopathologic criteria, but mainly to focus on the “clinical” issue, providing clinicians practical recommendations on the interpretation of the clinical and dermoscopic characteristics of Spitzoid lesions and on the management decision.

Age is crucial

As strongly supported by existing data, the most crucial parameter in the evaluation of Spitzoid lesions is age. Specifically, the possibility that a Spitzoid-looking lesion is a melanoma linearly increases after puberty, while it is extremely low before 12 years of age. This has led to the recommendation that a Spitzoid-looking lesion developing in the postpubertal age should be excised to exclude melanoma. The threshold of 12 years is supported from statistical and epidemiological considerations. Particularly, by applying Bayes’s rule to differentiate between Spitz/Reed nevus and melanoma, Vollmer et al.16 showed that the a priori possibility to diagnose Spitz/Reed nevus vs melanoma is high in subjects under 12 years of age, sharply decreasing after this threshold.

Actually, the discrimination of patients with Spitzoid lesions in 2 age groups is also supported by different clinical and dermoscopic characteristics between them. In detail, Spitzoid lesions in prepubertal children usually exhibit a more typical morphologic aspect and clinical course. Nevi deviating the typical morphologic criteria or undergoing unexpected evolution and, thus, prompting clinicians to excise them, are uncommon in this age group. In contrast, Spitzoid lesions in individuals after puberty are often more troublesome to interpret from a clinical and dermoscopic point of view. Surgical excision of Spitzoid lesions is the rule in the latter age group, but even histopathologic examination may be insufficient to establish an accurate diagnosis.

Although age represents a crucial parameter in the interpretation of Spitzoid lesions, this should not mislead clinicians to underestimate cases of prepubertal melanoma. Pediatric melanoma, albeit uncommon, does exist and its early diagnosis and appropriate management have a substantial impact on patient’s health. Effectively, the dual goal of clinicians when evaluating spitzoid lesions under the age of 12 is not to miss the rare cases of melanoma,
while minimizing the rate of nevi misinterpreted and managed as melanoma. The latter is particularly relevant since melanoma management includes surgical procedures with significant burden on patient’s health, such as the complete lymph node dissection following a positive sentinel lymph node biopsy. Especially in childhood, both under- and over-diagnosis of melanoma result in important physical, social, ethical and legal consequences.

**Dynamic of Spitzoid lesions**

The benign natural evolution of Spitz/Reed nevus is well-documented, while few described cases of metastatic diffusion with deadly outcome were more likely melanoma not accurately diagnosed. Typically, after a rapid growth phase, Spitz/Reed nevus stabilizes and gradually enters an involutive process. This evolution characterizes both pigmented and amelanotic forms and partially explains the reason why Spitz/Reed nevi are uncommon in adults, making the detection of a Spitzoid lesion in the adult age even more alarming. Effectively, given that a Spitz/Reed nevus showing “typical” aspects in prepubertal age is likely to regress spontaneously, only follow-up should be deemed necessary. A surgical excision should be considered only in case of peculiar clinical and/or dermoscopic characteristics that do not fit the typical aspect of a Spitz/Reed nevus. Avoiding unnecessary surgical procedures is particularly useful in children, considering that the pediatric patient generally shows little compliance to surgery, often requiring general anesthesia or sedation. Moreover, surgery entails the risk of complications and unaesthetic scars that may turn out to be problematic in the adult age. Postsurgical complications might be significantly more severe in case of sentinel lymph node biopsy, which may result positive in Spitz/Reed nevi, and especially in case of completion lymph node dissection. Finally, legal consequences cannot be ruled out if the surgical procedures were based on no other indication than the diagnosis of a typical Spitz/Reed nevus.

**Size of the lesions**

The decision to excise a Spitzoid lesion in the pediatric age should be based on the presence on morphologic or evolutorial parameters that exceed standards of “relative normality”.

The first factor reported is the size, with lesions exceeding 8 mm of larger diameter warranting excision. The diameter of Spitz/Reed nevi is usually equal to or less than 6 mm, while a growth beyond 10 mm has been reported in the literature as uncommon and suspicious. An intermediate value of 8 mm constitutes an acceptable threshold and has been considered a valid discriminant dimensional factor in previous studies.

**Palpability**

Nodular spitzoid lesions merit special attention. A nodular lesion of recent onset is by definition suspicious, especially when it dermoscopically lacks the characteristic regular distribution of monomorphous dotted vessels that typifies Spitz/Reed nevus. Although large irregular, polymorphous and asymmetrically distributed vessels have also been described in the context of Spitz/Reed nevi, the presence of the latter criteria is generally suggestive of melanoma. The presence of micro ulcerations is an additional warning sign, as they indicate a thinning of the epidermis due to the rapid proliferation of the underlying lesion.

**Dermoscopic patterns**

Dermoscopically, Spitz/Reed nevi display two predominant patterns, namely globular and starburst. The former is more frequently associated with Spitz nevi while the latter characterizes Reed nevi, even though this distinction, as explained above, might be practically irrelevant. Less common dermoscopic patterns include the homogeneous black pattern, the homogenous pink pattern (characterized by dotted or irregular vessels), and the inverse network pattern. The latter is characterized by interconnected hypopigmented serpiginous lines which form a network that circumscribes irregular pigmented globular-like structures or dotted vessels and which can be associated with crystalline or chrysalis structures. However, in about 20% of cases, Spitz/Reed nevi may dermoscopically exhibit a multicomponent or atypical pattern, characterized by an asymmetric distribution of structures and colors and by pigmentation
structures similar to the white-blue veil. The evidence of asymmetric growth is often considered an indicator of histopathologic atypia.

The frequency of different dermoscopic patterns of Spitz/Reed nevi and their histopathologic correlation was investigated by Ferrara et al. The authors found a higher frequency of the globular pattern in the “classic-desmoplastic” Spitz nevus, while the starburst pattern was more typical of pigmented Spitz nevus, Reed nevus and Spitz/Reed nevus. An important finding of the latter study was the high frequency of the “multicomponent” pattern among histopathologically atypical Spitz nevi. Pellacani et al. investigated the correlation among dermoscopic, histopathologic and confocal microscopic findings of Spitz nevus, Clark nevus and melanoma. According to their results, the most frequent dermoscopic patterns of Spitz nevi were the starburst, the globular, and the multicomponent, followed by the reticular/homogeneous and the inverse network pattern. Of note, a reticular/homogeneous or a multicomponent pattern was observed mostly in lesions suggestive of melanoma by means of confocal microscopy.

Location

Although there is no evidence that the risk of melanoma depends on the anatomical site, the management of Spitzoid lesions might also be influenced by their localization on specific body sites. First, we recommend the excision of lesions located on anatomical sites not typical for a Spitz/Reed nevus according to what has been reported in the literature and observed in the clinical practice (head, neck, lower limbs). Our recommendation is in agreement with other investigators suggesting excision of scalp, acral and genital Spitzoid lesions, because they are often associated with cytologic and architectural atypias. Furthermore, in our experience, Spitzoid lesions on special body areas often deviate the usual dermoscopic features of Spitz/Reed nevus, complicating the clinical diagnosis and management. For instance, the specific anatomic architecture of the acral skin might result into an atypical dermoscopic pattern of an acral Spitz nevus, posing significant problems in its accurate diagnosis and regular follow-up.

In addition, early surgical excision of Spitzoid lesions located on surgically troublesome body sites, such as the nose or the eyelids, might also be recommended. This suggestion is based on the experience of our group and aims to prevent more complicated surgical interventions that would be required if the lesion grows during follow up.

Special variants

Finally, we recommend excision of lesions whose clinical and/or dermoscopic characteristics are suggestive of a “special” Spitz variant (i.e., verrucous, desmoplastic, and angiomatoid). The clinical management of these subtypes might be troublesome, as they often deviate from the “standard” diagnostic criteria and natural course of Spitz/Reed nevus. In a previous study, we excised a verrucous nevus showing several typical criteria (dotted vessels, inverse network) but displaying a global architecture not fitting the diagnosis of Spitz/Reed nevus. Similarly, a combined lesion consisting of a Spitz/Reed nevus and a common nevus described by Duncan et al. was histopathologically characterized by a high degree of cytologic atypia, increased cellularity, loss of symmetry and an increase of mitotic figures.

Conservative approach in children

According to our recommendations, a conservative management strategy should be applied in the vast majority of Spitzoid lesions in childhood. However, we strongly recommend their regular follow-up in order to enable the detection of spitzoid melanomas that may appear small and morphologically regular at baseline visit, but exhibit signs of irregular or excessive growth during monitoring. In line with previous evidence, we suggest a 3 to 6 month period as the optimal follow up interval.

An excessive dimensional growth (beyond 8 mm), a tendency not to stabilize (typically, the appearance of globules of different dimension and color), or the detection of one or more of the previously described morphologic features at any time during follow-up, should warrant excision of the lesion.

As mentioned above, the expected evolution of Spitz/Reed nevi includes a stabilization phase followed by a slow involution until their disappearance. Therefore, in children younger than 12, a Spitz nevus showing “typical” aspects should be dermoscopically monitored until its stabilization, which often
Conclusions

Spitzoid lesions are a diagnostic challenge for dermatologists, since they represent a group of morphologically similar entities whose biological behavior ranges between the benign Spitz/Reed nevus and the potentially lethal spitzoid melanoma. The studies carried out in the last few years have only partially clarified the discrepancies on interpretation of atypical Spitzoid lesions. The advances of immunohistochemical and biomolecular techniques have so far been able to shed light to the controversy and provide clinicians with useful information for the diagnostic approach and appropriate management of Spitzoid tumors.

Based on existing evidence and our experience, we aimed to provide decision-making criteria that could enhance clinicians to adopt a more homogeneous diagnostic and management path of Spitzoid tumors.
References


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Cyclosporine (cyclosporine A, CsA), was first isolated from the soil fungus Tolypocladium inflatum in 1970.\(^1\) Its antifungal activity was demonstrated to be poor, whereas a potent immunosuppressive effect was found in 1976.\(^1\) For this reason, two years later, CsA was successfully used in preventing kidney transplant rejection\(^2\) and, in 1979, it was proven effective in the treatment of rheumatoid arthritis and psoriasis.\(^3\) The original orally administered formulation of CsA (Sandimmun, Novartis) was approved in 1983 by the Food and Drug Administration (FDA) for the prevention of transplant rejection.

Despite the increased availability of new therapeutic options, CsA is still one of the most widely used and effective systemic drugs for the treatment of psoriasis and atopic dermatitis, worldwide.\(^4\)-\(^6\) In Italy, it has been found to be the most frequently used systemic antipsoriatic therapy.\(^7\)

It is noteworthy that the Italian experience in CsA is broad, and often long lasting, for most of its therapeutic indications, starting from transplant with 25-year experience. Moreover, several indications for CsA have originated from clinical trials conducted in Italy.
Upon these grounds, an Italian Consensus Conference was held to provide recommendations based on real-world clinical experience.

Pharmacokinetics

CsA is a cyclic endecapeptide,8 able to act directly on cells of the immune system, primarily on T cells, because of its inhibitory effects on calcineurine. It targets the major T cell-driven pathways of immune-mediated response and inflammation. These effects explain its efficacy both in prevention of transplant rejections and in immune-mediated dermatoses.9

CsA absorption occurs within 30 minutes and the peak serum concentration (Cmax) is observed 2-4 hours after the administration.10-15

Due to its lipophilicity, CsA is widely distributed throughout the body. In plasma, it is mostly bound to lipoproteins (≥90%) and easily transferred between different lipoproteins, and to or from albumin as well.5 It has a first-pass effect of 27% in the liver.15

CsA metabolism is highly dependent on cytochrome P450 isoenzymes 3A4 (CYP3A4) and 3A5 (CYP3A5) in the liver and small intestine, and dependent on the efflux p-glycoprotein pump (PGP) encoded by the multidrug resistance-1 gene (MDR1) in the gastrointestinal tract and liver.5 The metabolites of CsA are mainly excreted in the bile; another 6% is eliminated in the urine, of which 0.1% remains unchanged.12

A higher CsA serum concentration reflects higher clinical efficacy and is obtained if the drug is administered before food intake.5,16

CsA dosage is established on a weight-per-weight basis (mg/kg/day, see below for further details).

Drug interactions

By virtue of its almost complete hepatic metabolism by cytochrome P450 IIIA, the plasmatic levels of CsA are increased or decreased by drugs that inhibit or stimulate cytochrome P450 activity, respectively (Tables I-III).5 The consequent change in CsA bioavailability results in adverse effects that are potentially exerted on target-organ toxicity.17

Among patients with dermatoses, the use of some systemic antibiotics as well as of NSAIDS could be critical due to pharmacological interactions, leading

### Table I.—Drugs and foods that inhibit the cytochrome P450 system, leading to a higher concentration of cyclosporine.5

- Allopurinol
- Amiodarone
- Antifungals (fluconazole, itraconazole, ketoconazole and voriconazole)
- Bromocriptine
- Calcium channel blockers (diltiazem, nicardipine, verapamil and mibepradil)
- Ciprofloxacin
- Danazol
- Doxycycline
- Furosemide
- Gentamicin and tobramycin
- Grapefruit juice
- Macrolide antibiotics (erythromycin, clarithromycin and josamycin)
- Methylprednisolone
- Metoclopramide
- Oral contraceptives and androgen steroids
- Protease inhibitors
- Ranitidine and cimetidine
- Statins (especially atorvastatin and simvastatin)
- Ticarcillin
- Warfarin

### Table II.—Drugs that stimulate the cytochrome P450 system, leading to a lower cyclosporine level.5

- Anticonvulsants (carbamazepine, phenobarbitone, phenytoin and valproate)
- Isoniazid
- Metamizole
- Nafcillin
- Octreotide
- Orlistat
- Pro布col
- Rifabutin
- Rifampicin
- Selective serotonin reuptake inhibitors (sertraline)
- St John’s Wort (Hypericum perforatum)
- Sulfinpyrazone
- Terbenafine

### Table III.—Drugs that may impair renal function during cyclosporine treatment.5

- Acyclovir
- Aminoglycosides (gentamycin and tobramycin)
- Amphotericin B
- Cimetidine and ranitidine
- Ciprofloxacin
- Colchicine
- Fibrates
- Melphalan
- Methotrexate
- Nonsteroidal antiinflammatory drugs
- Trimethoprim with sulfamethoxazole
- Vancomycin
The clinical benefit of CsA therapy is related not only to the clinical response, but also to the effects on psychological distress, which are a common experience in patients with psoriasis (see below).29, 30 Many studies indicate a clear dose-dependent response, with higher doses producing higher rates of remission.6, 31-35

To identify patients who may benefit from systemic treatments including CsA, the “rule of tens” has been proposed: a body surface area affected >10% or a Psoriasis Area Severity Index (PASI) >10 or a Dermatology Life Quality Index (DLQI) >10.36

Dose-finding studies and current consensus guidelines have identified 2.5 mg/kg/day CsA as ideal starting dose, to be gradually increased up to 5 mg/kg/day by 0.5-1 mg/kg/day at 2-4 weeks intervals.4, 21-32 Tachyphylaxis did not occur if regimens with progressive increases were prescribed.31 In patients who are unresponsive, or who respond inadequately after 3 months (PASI 50 not achieved), CsA withdrawal is recommended.4 Drug reduction should be performed stepwise (0.5-1.0 mg/kg/day at 2 weeks intervals).4

Based on long-term clinical experience, six therapeutic strategies are currently used to treat moderate-to-severe psoriasis with systemic CsA (I=induction; M=maintenance; definition and treatment regimens are illustrated in Table V): 1) intermittent short-term therapy (I); 2) rescue therapy (I); 3) long-term continuous therapy (I+M); 4) combination therapy (I+M); 5) rotational therapy (I+M); and 6) week-end therapy (M).4, 6, 37, 38

CsA has been proven effective in all variants of psoriasis (Table IV), where different schemes in terms of doses and treatment duration have been used.4, 6, 20

### Table IV:—CsA in psoriasis variants.


### Table V.—Systemic cyclosporine treatment schedules.

| Intermittent short-term therapy | Short course (12-16 weeks) until significant improvement is achieved, after which treatment is withdrawn |
| Rescue therapy | Used in severe flares of disease until an alternative maintenance treatment is instituted |
| Long-term continuous therapy | Clinical improvement maintained with the lowest effective dose |
| Combination therapy | Cyclosporin can be combined with topical therapies, such as corticosteroids, anthralin, or vitamin D3 analogues, and other systemic treatments, such as methotrexate, fumaric acid esters and mycophenolate mofetil |
| Rotational therapy | Treatment with cyclosporine can be rotated with other systemic agents (see text) |
| Week-end therapy | Maintain remission (5mg/kg/day) for 2 consecutive days a week for 24 weeks |
Moreover, CsA due to its fast therapeutic action, represents an appropriate “bridging” therapy, which is useful if associated with a new long term biological treatment which needs a certain time lapse to be effective.4,21

INTERMITTENT SHORT-TERM THERAPY

The most common systemic CsA regimen is represented by a short course (12-16 weeks) administration, followed by the withdrawal when a significant improvement (PASI 75) or remission (PASI≥90) is achieved. In case of relapse, a short-term course may be repeated at the previously effective dose.4, 21, 23, 39-43

In patients with severe psoriasis, a 1-year remission is obtained in 80% of cases with 2 courses of therapy, the remission after the first course lasting 4 months in 45% of cases.41, 42 A slight advantage in terms of remission duration was observed with dose tapering.41, 42

RESCUE THERAPY

The rapid onset of effect with short-term CsA is useful to control severe flares, particularly in severe psoriasis variants.4 A starting dose of 5 mg/kg/day is recommended, followed by a gradual dose decreasing after remission.13,14,17

LONG-TERM THERAPY

Long-term continuous therapy with CsA is a less common approach for severe psoriasis and is prescribed to obtain a significant clinical improvement with the lowest effective dose rather than a complete control.15,44-47 Its duration is limited to 2 years in Europe 9, 20,21 with the possibility of a further prolongation in selected cases, and to 1 year in the United States.48 The typical maintenance dose is 3-3.5 mg/kg/day.49

COMBINATION THERAPY

The effects of systemic CsA associated with various topical treatments, as corticosteroids,50-52 anthralin,53 vitamin D3 analogues,54 or systemic treatments, as methotrexate,55 fumaric acid esters,56 acitretin,57 or mycophenolate mofetil 58 have been evaluated only in small case series and single case-reports.4 The main advantage of combination therapy is the possibility to minimize toxicity due to the dose reduction,4 even if the possibility of adverse effects arising from pharmacological interactions has to be taken into account.6

A recent Italian study reported a clinical response (therapeutic success or complete clinical remission) in 80% of patients with moderate-severe plaque psoriasis who received CsA plus systemic methotrexate or retinoids, or plus topical treatment and/or phototherapy.59

ROTATIONAL THERAPY

CsA treatment of psoriasis is not associated with tachyphylaxis,4, 20, 51, 60, 61 allowing rotational therapy, whose rational is similar to that of combination therapy, characterized by the sequential use of the above mentioned systemic agents.20, 61, 62

An Italian study has proven, in patients with severe psoriasis, the superiority of the sequential therapy with CsA (3 mg/kg/day for 4 weeks) and narrow-band UVB phototherapy compared to narrow-band UVB phototherapy alone.63

WEEK-END THERAPY AND PULSE THERAPY

An additional therapeutic maintenance schedule was proposed and evaluated by PREWENT (Psoriasis Relapse Evaluation with Week-End Neoral® Treatment) study, a 24-week, double-blind placebo-controlled trial, carried out in 22 Italian hospitals or university Dermatology units. CsA microemulsion was used in patients with chronic plaque psoriasis who had achieved clinical remission after continuous CsA therapy, and then randomized to receive oral CsA 5 mg/kg/day or placebo for two consecutive days/week for 24 weeks. Time to first relapse (adopting PASI as diagnostic criterion) was significantly longer with CsA and PASI was significantly lower at weeks 4-16 in CsA recipients. The incidence of adverse events was similar in both groups.37

Similar results have been reported by another Italian study, in which patients with severe chronic plaque psoriasis were assigned to a continuous schedule or 4-day therapy per week, administered for 6 months. PASI score and severity of itching were efficiently controlled in both groups. Moreover, the safety profile was shown more favourable in the group with intermittent 4 days per week administration.64
**Consensus Conference Statements**

— There is consensus on the **indications** reported by literature for the treatment of psoriasis variants, in particular for the doses and the duration of therapy.

— However, in clinical practice, indications to start CsA treatment are less strict. It may be used in the following cases with PASI<10:
  - resistance to topical drugs (experience suggests that resistance may occur even with PASI≥5);
  - certain clinical characteristics, *e.g.* the site of the disease (palmoplantar psoriasis, genital psoriasis);
  - characteristics of the patients, including sex, age, personal or social relationship and employment. In fact, the impact of psoriasis on a patient’s quality of life (QoL) may be disproportionate to the clinical severity, due to his/her self-perception and his/her expectations about the treatment. Due to the young average age of psoriatic patients, the consequences of the psychological and emotional stress are particularly relevant in terms of their impact on social and sexual life leading to low self-esteem, high anxiety, and sexual dysfunction.

— In limited extent psoriasis, *e.g.* nail psoriasis where PASI and NAPSI (NAil Psoriasis Severity Index) may result quite low: CsA may be considered even if it is not the first-line treatment. The indication has to be established on the basis of the patient’s characteristics (*e.g.* personal relationship and employment). In clinical experience, CsA has proven effective when the ungual variant was associated to generalized involvement.

— A weight-per-weight **dose**, based on the ideal body weight is recommended. Adopting as a reference the actual body weight, overweight or obese patients may be exposed to high doses, even double that those of normal weight patients, with an increased risk of toxicity (see below for further details). In order to obtain a better compliance with the therapy, a fixed dose (200 mg/day) may be used in such patients.

— To establish the optimal dose, the clinical severity has to be taken into account: for PASI higher than 20 and especially in cases with a relevant inflammatory component, an induction dose of 5 mg/kg may be appropriate; a dose of 2.5 mg/kg/day, although reported in clinical trials, has to be considered suboptimal in severe psoriasis.

— Based on our experience, a satisfactory control of itching is generally obtained in few weeks, generally earlier than the control of skin lesions.

— The clinical response has to be assessed after the first month, when both the profiles of efficacy and safety (see the section Management of patients) should be assessed. The treatment has to be carried out for at least 3 months, evaluating side effects.

— After clinical remission is achieved, multiple possibilities can be evaluated about which the Consensus doesn’t express a unanimous recommendation, rather the advice to make a choice according the individual patient’s characteristics, clinical history, and needs:
  - tapering after 3 months of treatment or
  - tapering once PASI 0 has been reached or
  - once PASI 0 has been reached, maintenance therapy for 1 month/or at least 1 month due to the high risk of relapse.

— When a relapse occurs:
  - during the tapering, then the full dose regimen is recommended followed by continuous therapy for 6 months
  - immediately after/close to the treatment completion (unlikely possibility), the rotational therapy may be an option (see below)
  - few months after the treatment completion, the treatment can be repeated, according to the disease extension and the severity of the relapse.

— CsA **high doses** (5 mg/kg/day) may be used also to control severe flares.

— The recommended dose for induction is ≥3 mg/kg/day

— The recommended dose for long-term therapy is 3 mg/kg/day.
Atopic dermatitis is one of the most common chronic relapsing childhood dermatoses which affects up to 30% of children in most cases before the age of 5 years, but persists into adulthood in more cases than reported by the literature (up to 3%). Moreover, its onset may be observed in adult age, even in elderly patients. Overall, clinical experience suggests that atopic dermatitis is by far more frequent than expected according to diagnostic criteria.

In the diagnosis of atopic dermatitis several criteria have been established, but there is no laboratory biomarker.

Current management of atopic dermatitis has not curative targets, while it is focused on symptoms relief. CsA is the only immunosuppressant agent approved in Europe for the short-term treatment of severe atopic dermatitis that cannot be controlled with topical therapy. It has not been formally approved by FDA for this indication, but it has been recommended by American Academy of Dermatology (AAD). There is no statement indicating the recommended dose in atopic dermatitis, although the therapeutic dosage used in psoriasis is conventionally administered.

The data of a systematic review clearly demonstrated the efficacy of CsA in atopic dermatitis. Body surface area, erythema, sleep loss and corticosteroid use were reduced in the CsA group. A 47% improvement in itching has been described within 2 weeks in patients treated with high dose of CsA.

Short-term therapy

According to the European guidelines, an initial dose of 5 mg/kg/day for 2 weeks has to be gradually tapered to a dose of 1.5 mg/kg/day over 3 months, based on the individual clinical response.
A meta-analysis by Schmitt demonstrated the effectiveness of short-term continuous CsA treatment (50% reduction in severity after 6-8 weeks of therapy). Patients treated with an initial dose of 4-5 mg/kg/day showed a more rapid response at 2 weeks (40% decrease in severity) in comparison to patients treated with a lower initial dose of 2.5-3 mg/kg/day (22% decrease in severity). Nevertheless, after a 6-8 week follow-up, no difference was observed between the two doses in terms of responses.

According to results of a recent double-blind randomized, multicentre trial, CsA is superior to prednisolone in inducing a stable remission of severe eczema.

**Long-term therapy**

On the basis of the above mentioned results, the lowest effective dose is recommended if a maintenance therapy is needed.

Two randomized controlled studies reported the effect of CsA long-term therapy to control severe atopic dermatitis. In a pediatric population (2-16 years), intermittent short-term therapy (5 mg/kg/day) for 12 weeks was compared to a continuous 1-year course (5 mg/kg/day), the latter being associated to better outcomes in terms of short-term and sustained clinical response and patients’ QoL.

The second study, which was performed in patients with severe atopic dermatitis, compared two long-term CsA regimens: an initial dose of 5 mg/kg/day tapered to 3 mg/kg/day as tolerated vs 3 mg/kg/day increased to 5 mg/kg/day as needed, both maintained the optimal dose for the following 10 months.

After 1 year, patients in the treatment group who started with 5 mg/kg/day showed slightly better results in terms of disease control (59.8% vs. 51.7%), and similar adverse events.

Considering relapse and worsening after CsA, data reported is highly variable, in terms of rates and time of occurrence. However, there is no evidence of a rebound phenomenon on this drug withdrawal.

**Consensus Conference Statements**

(Recommendations for adult patients with atopic dermatitis)

— When treating atopic dermatitis, a crucial point is the relevant impact of the disease on QoL.

QoL scores should be used in conjunction with objective measures of severity as an assessment tool. Because of the rapid onset of action and marked efficacy, CsA is particularly useful in the treatment of atopic dermatitis.

— Atopic dermatitis is often associated to severe itching, whose significant improvement is generally obtained in 1-2 weeks with CsA.

— In the management of atopic dermatitis skin care, cleansing and bathing, lifestyle, diet restriction with avoidance strategies are important factors. Patients have to be informed and instructed in order to actively and effectively collaborate.

— With short-term therapy, a high initial dose (4-5 mg/kg/day) is recommended to obtain a more rapid and sustained improvement.

— With long-term therapy, the minimum effective dose of CsA to achieve substantial improvement in disease severity is appropriate.

— The duration of treatment able to obtain a satisfactory clinical response (4-6 months) is longer than that indicated in clinical guidelines (2-3 months).

**Impact of CsA on QoL**

Dermatoses cause as much disability as that of other major medical conditions. For instance, disability from psoriasis is comparable to that from arthritis, hypertension and diabetes, while QoL from atopic dermatitis is impaired to a similar extent as is seen in other common childhood diseases, such as asthma and diabetes.

The impact on patient’s QoL of dermatoses such as psoriasis and atopic dermatitis is relevant and has been shown able to affect the adherence to medication. Consequently, QoL assessment tools have been specifically developed for dermatologic conditions (e.g. the Dermatology Life Quality Index, DLQI, the Psoriasis Disability Index, PDI, the Eczema Disability Index, EDI, and the Psoriasis Index of Quality of Life, PSORIQoL). In addition, the updated “rule of tens” used to select patients with severe psoriasis who could benefit from systemic treatment includes QoL parameters.

The impact of a dermatological condition on QoL doesn’t show a clear relationship with the clinical severity of the disease, as assessed with PASI and depends more on patient’s self-reported morbidity.
The adherence to dental hygiene has to be recommended and checked at 6-months periodic examinations.5, 6

Laboratory tests have to be performed both at baseline and during the treatment. They include serum creatinine, potassium, magnesium, bilirubin, liver enzymes, uric acid, fasting lipids, urea nitrogen, blood cell count, and urine analysis.21, 61 According to the international guidelines, the tests have to be repeated during CsA treatment at definite intervals (every 2 weeks during the first 2 months of treatment).6, 20-22

The physical examination should include blood pressure measurement, at least in two separate occasions basally, and continuous monthly monitoring during the treatment.5

Due to a variety of pharmacological interactions (Tables II-IV), it is crucial to investigate the use of any systemic drug (over-the-counter drugs included) before initiating a treatment with CsA, and to reiterate the investigation at each visit, eventually mentioning the specific class of medication.

Notably, evidence suggests that CsA is able to inhibit in vitro HCV replication. Some data confirm this property in vivo, in patients who underwent liver transplantation or with chronic active hepatitis.90, 91 The Italian experience on patients with concomitant rheumatologic disorders and HCV infection indicates that CsA is effective and safe, and may contribute to better outcomes.92, 93 Moreover, the short-term therapeutic association of CsA and anti-TNF shows a satisfactory safety profile (Table VI).91-93

In patients with dermatoses, CsA has been shown able to improve QoL. Considering psoriasis, data of a 1-year substudy from PISCES (Psoriasis Intermitent Short Course of Efficacy of Sandimmun Neoral) has demonstrated an improvement in QoL (P<0.001) and a reduction in itching and disease extent/severity (P<0.001 for both).87 Similar results have been observed for atopic dermatitis both in adults 74, 88 and in children.80

Considering the common experience of psychological distress in patients with psoriasis, generally with a higher burden in female patients, the PSYCHAE study, a large observational study performed in 39 Italian dermatology centers on more than 1500 patients, has shown that, differently to methotrexate and topical corticosteroids treatment, CsA treatment is able to control the risk of psychological distress assesses using the General Health Questionnaire (GHQ) and the Brief Symptoms Inventory (BSI).29, 30 It is interesting to note that only 16% of physicians in the PSYCHAE trial declared that they considered a patient’s psychological status when choosing a systemic therapy for psoriasis.30

Management of patients treated with systemic CsA

CsA is the most commonly used drug by Italian dermatologists for the treatment of moderate-severe psoriasis and atopic dermatitis unresponsive to conventional therapy.7 However, due to its narrow therapeutic window, clinicians have to take into account the multiple pharmacological interactions, and the relevant influence of comorbidities on therapeutic strategy.89

Clinical evaluation

Before starting CsA treatment, a careful clinical evaluation has to be carried out (history, examination, baseline laboratory examinations).5, 61

Among comorbidities, previous or concurrent malignancies, hypertension, renal impairment, current infections, or a history of previous PUVA phototherapy have to be investigated.5, 61 Skin surface should be inspected in order to identify the presence of cancerous or actinic lesions. In case of active herpes simplex infection or viral warts the treatment should be postponed after healing.5, 61

Hepatitis profiles including anti-HAV, HBsAg, anti-HBs, anti-HBe, anti-HCV and also anti-HIV should be checked in patients treated with CsA.61
Contraindications

CsA is contraindicated in uncontrolled hypertension, renal disease, serious infections, and in patients with a previous history of malignancy (excluding basal cell carcinoma).\(^5\),\(^20\)-\(^23\),\(^78\)

Moreover, the drug should be avoided in patients previously treated with a high cumulative dose of psoralen and ultraviolet A light phototherapy (PUVA), due to the risk of carcinogenicity.\(^5\),\(^46\)

Skin infections superimposed to atopic eczema do not represent an absolute contraindication, but an adequate antibiotic therapy is needed before CsA.\(^78\)

A careful evaluation of the benefit/harm balance is requested in patients with epilepsy, severe hepatic dysfunction, immunodeficiency disorders, diabetes, obesity, premalignant conditions. Elderly patients (≥65 years), patients with a history of drug or alcohol abuse, poor compliant patients are at higher risk to develop adverse events.

For CsA use in pregnancy and lactation, see below.

Consensus Conference Statements

— There is consensus on the following absolute contraindications:
  - poorly controlled hypertension,
  - severe infections,
  - malignancies (ongoing disease or previous history; particular caution with haematological malignancies and dermatological malignancies, with the exception of basal cell carcinomas)

— There is consensus on the following relative contraindications:
  - liver impairment,
  - concomitant administration of drugs able to pharmacologically interact with CsA (see above),
  - concomitant PUVA (also previous PUVA treatment at dose >1000 J/cm²),
  - pregnancy and lactation (for more details, see below),
  - antihypertensive treatment with a combination regimen of two or more agents

Management of adverse effects

The concern about adverse effects of CsA has limited its use also in dermatology, although the doses used to treat skin diseases are largely beneath those

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### Table VI.—Laboratory examinations during cyclosporine treatment.

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Pretreatment</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(erythrocytes, leukocytes, platelets)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>(transaminases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes (sodium, potassium)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine analysis and sediment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Uric acid</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cholesterol, triglycerides</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Further specific test may be required according to clinical signs, risks and exposure.*
Renal impairment

Renal dysfunction associated to CsA therapy may be functional or structural. Its occurrence and characteristics are largely dose-dependent, damage being more frequent and more likely to become structural with prolonged therapy (over 2 years) or doses (higher than 5 mg/kg/day which is considered the highest recommended dermatological dose, i.e. up to 8-8.5 mg/kg/day which were used in the past in transplant recipients).

Kidney impairment, based on either vascular or tubular alterations, may lead to a decrease in renal glomerular filtration rate (GFR) and in renal blood flow (as reflected by a decreased creatinine clearance) leading to hypomagnesaemia, decreased bicarbonate concentration, hyperuricemia, and hyperkalemia.

At lower doses, as those administered with intermittent short-term therapy, nephrotoxicity causes functional changes and is reversible on drug withdrawal. Long-term and/or high dose CsA therapy is a risk factor for tubular interstitial fibrosis which is mediated by an increase in Transforming Growth Factor-beta (TGF-β) and is facilitated by older age, concurrent hypertension or obesity.

Recommendations about prevention, monitoring and management of renal nephrotoxicity following the S3-European guidelines and an international statement consensus are reported in Figure 1. The best predictive factor of nephrotoxicity is the percentage of serum creatinine increase over baseline values.

Factors likely to increase the risk of nephrotoxicity (e.g., advanced age, diabetes, nephrotoxic drugs, obesity) should also be evaluated, and medication charts should be carefully reviewed for potential drug interactions.

A difference is apparent between US and European guidelines with respect to the duration of continuous treatment to prevent chronic nephrotoxicity: a maximum of 1 year is recommended by the American guidelines, with the exception of female and pediatric patients, and is reversible. — Serious adverse effects are reported with limited frequency, but need careful and appropriate management.
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are the laboratory tests of reference. Following this flow chart, i.e. decreasing the CsA dose by 25% if creatinine rises 30% over baseline and by 50% if the rise is ≥50%, the incidence of CsA nephrotoxicity is rather low and reversible. Estimated glomerular filtration rate (eGFR, to be estimated using Cockroft Gault) is not a routine laboratory measure and may be evaluated when serum creatinine is increased.

— Among agents able to increase nephrotoxicity, aminoglycosides, amphotericin B, ciprofloxacin, vancomycin, lovastatin, cimetidine, acyclovir, and NSAIDs have to be mentioned.

Figure 1. — Management of nephrotoxicity.22

Figure 1. — Management of nephrotoxicity.22

Consensus Conference Statements

— There is consensus on the flow chart proposed by the international guidelines (Figure 3).
— Serum creatinine and blood urea nitrogen

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Hypertension

The incidence of new-onset hypertension with CsA treatment ranges from 0% to 57%, being higher with a long-term treatment and lower with short-course therapies and reversible after dose reduction and/or withdrawal or with the use of antihypertensive drugs.5, 20, 41, 61, 76 However, some studies show the lack of a clear relationship between CsA dose and frequency of hypertension occurrence,5, 61, 100 thus suggesting a role for an individual variability in the sensitivity to CsA hypertensive effect.5, 100 This hypothesis supports the use of antihypertensive drugs rather than a reduction of the dose to manage the onset of hypertension.100

The differences observed between patients with atopic dermatitis (lower incidence) and with psoriasis (higher incidence) may be explained by their younger age and the increased association of obesity, respectively.5, 102, 103 A regular monitoring of blood pressure is crucial in patients with psoriasis, as they are known to be at increased risk of cardiovascular morbidity and mortality.104

A flow-chart reporting the recommendations from current guidelines about the management of hypertension

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The onset of hypomagnesaemia, which occurs earlier than that of hyperkalaemia, is a good even if poor predictor of renal impairment. Several conditions (e.g. administration of diuretics and aminoglycosides or alcohol consumption) are able to induce hypomagnesaemia, which favours nephrotoxicity. The daily recommended intake of magnesium is 400-420 mg. A list of magnesium rich foods is presented in Table VII

**Table VII.**—Magnesium-rich foods.101

<table>
<thead>
<tr>
<th>Food</th>
<th>Mg (mg/hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried almonds</td>
<td>264</td>
</tr>
<tr>
<td>Dried beans</td>
<td>170</td>
</tr>
<tr>
<td>Dried nuts</td>
<td>160</td>
</tr>
<tr>
<td>Whole wheat flour</td>
<td>120</td>
</tr>
<tr>
<td>Spinach</td>
<td>60</td>
</tr>
<tr>
<td>Potatoes</td>
<td>38</td>
</tr>
<tr>
<td>Chicken breast</td>
<td>32</td>
</tr>
</tbody>
</table>

Figure 2.—Management of hypertension.22, 61
Hyperlipidemia

Hyperlipidemia has to be carefully monitored and controlled with diet or medications (Figure 3). However, caution is needed with the co-administration of CsA and statins to detect myopathy (rhabdomyolysis) at an early stage. Cases of muscle toxicity have been reported with pravastatin, atorvastatin and lovastatin. Fluvastatin is the most studied and recommended lipid-lowering drug.

Associated to CsA treatment is reported in Figure 2. The choice of the antihypertensive drug is of particular interest and somewhat controversial both in literature and in clinical practice. Calcium channel blockers are the first choice thanks to their vasodilating effect, conferring some protection against nephropathy, although nifedipine should be avoided because of an increased risk of gingival hyperplasia. The calcium channel blockers of the dihydropyridine class, i.e. isradipine and amlopidine represent a good choice, since they do not modify CsA levels and exert a vasodilating effect on the afferent arteriole, which confers protection against nephropathy. Beta-blockers may also be used, taking into account the possibility of the disease worsening, while thiazide diuretics are contraindicated because of a potential increase in nephrotoxicity. Angiotensin-converting enzyme inhibitors and potassium-sparing diuretics should be avoided as they may cause hyperkalemia and a decrease in GFR.

The monitoring and control of hypertension, as well as of hyperlipidemia (see below) is crucial in patients with psoriasis because of their increased risk of cardiovascular morbidity and mortality.

Consensus Conference Statements

— There is consensus on the flow chart proposed by the international guidelines, although a closer monitoring is considered more appropriate, particularly at the beginning of the treatment (daily monitoring during the first week or with blood pressure levels ≥140/90 mmHg)

— To manage hypertension, there is consensus on calcium channel blockers as the first choice (excluding nifedipine for the increased risk of gingival hyperplasia; preferring isradipine and amlopidine because they don’t alter CsA levels). In clinical practice thiazide diuretics (even if contraindicated in renal impairment) are prescribed for short courses. Angiotensin-converting enzyme inhibitors (risk of hyperkalemia although associated to a protective vasodilating effect) and potassium-sparing diuretics (risk of hyperkalemia) are contraindicated

— If blood pressure levels are under control with a previously defined antihypertensive schedule, there is controversy about the need of any therapeutical change. In particular, angiotensin-converting enzyme inhibitors are not absolutely contraindicated if already included in the schedule. Considering the broad range of positions on this clinical question, it is highly recommended to seek the advice of a specialist consultant for a decision on any individual case

Malignancy

An increased risk of malignancy after long-term CsA treatment has been described in patients who underwent organ transplantation. A large review, investigating the incidence of malignancy in patients treated with CsA for up to 5 years for severe psoriasis, showed that the incidence of extracutaneous malignancy was not higher than that reported in the general population. CsA enhances the induction of skin tumours by UVA exposure. Actually, the risk of cutaneous squamous cell carcinoma (SCC) increases with longer duration of therapy, only in patients with a previous history
cases failed to show an increase in their incidence in patients treated for psoriasis.\textsuperscript{112, 115}

Infections

CsA administration may increase the general risk of bacterial, parasitic, viral, and fungal infections, as well as the risk of infection with opportunistic pathogens, but the actual incidence of infective complications when treating psoriasis is low.\textsuperscript{5, 20, 117} Management of infection depends on appropriate and prompt antibiotic therapy (for the choice of drugs, see drug interactions). In case of herpes simplex infections, CsA therapy should be deferred until resolutions.\textsuperscript{5, 20, 22}

Vaccinations given concomitantly with CsA may be less effective. Studies in patients with transplan-
Consensus Conference Statements

- When starting CsA, a baseline pregnancy test is not mandatory.
- CsA is contraindicated during pregnancy.
- Drug discontinuation is recommended when planning an intended gestation or when an unplanned gestation is ascertained.
- Clinical experience demonstrates a good safety profile for CsA:
  - cases of administration in neonatal or pediatric age without the evidence of adverse events.
  - approximately 700 pregnancies without negative adverse events in women who previously underwent organ transplantation.
  - there is no evidence of adverse events in pregnant women who did not discontinue CsA treatment during pregnancy.
  - there is no evidence of teratogenicity.
- Since no teratogenicity has been proven, CsA is of choice when a systemic drug is needed.
- Cases of premature delivery have been reported.
- CsA safety profile is better than that of alternative agents (e.g., etretinate administration has to be avoided for 2 years prior the conception).
- At present there are no adequate and well controlled studies in pregnant women and, therefore, CsA should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.
- Therapeutic abortion is not an absolute indication in case of exposure to CsA of a pregnant patient. The choice has to be made on the basis of an acceptable risk-to-benefit balance, providing the patient with the opportunity to make an informed decision and taking into account her individual needs and preferences.

PEDIATRIC USE

Children are less susceptible to CsA toxicity because of a reduction in drug bioavailability and a lower predisposition to nephrotoxicity. CsA has been used at high doses in pediatric transplant recipients and in children with atopic dermatitis or psoriasis with no serious adverse effects. There is evidence, even from small studies, of no adverse events associated to breastfeeding during CsA treatment.
Conscens Conference Statements

— CsA has been used starting from the first year of life and cases of high dose treatment in pediatric patients who underwent organ transplantation are described. However, caution is needed, when changes in standard schedules or guidelines are adopted
— CsA management in pediatric patients (usually to treat atopic dermatitis) needs specific considerations and caution, even if better tolerance is proven

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ALTOMARE

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Scabies acquired in Chinese massage centers

TO THE EDITOR: In the last few months, we have observed three patients who contracted scabies at Chinese massage centers. The case list is made up of three Caucasian males, aged 29, 46 and 56 years, respectively, in good general health, heterosexuals. All three patients were regular customers of Chinese massage centers (two of them used to attend the same center). A clinical diagnosis of allergic contact dermatitis and unsuccessful treatment with topical corticosteroids and oral antihistamines were made at other dermatological centers to all three patients.

Clinical history of the three was negative for previous scabies. History also allowed to exclude with certainty other possible sources of infestation (no intercourses, no direct contacts with patients affected by scabies, no direct contacts with fomites belonging to patients with scabies in the last six months before our examination). Latency time ranged from 3 to 4 weeks.

Clinical picture was typical: widespread, severe pruritus, and burrows and vesicular-papular lesions at interdigital folds, wrists, axillae, chest, abdomen, pubis, penis and buttocks.

Parasitological examinations were positive for mites, eggs and feces in all patients.

All patients were successfully treated with 5% permethrin cream (one single application followed by a second single application one week later). Topical methylprednisolone aceponate (2 applications/day for 10 days) and oral hydroxyzine (25 mg/day for 10 days) were necessary in two patients in order to control residual pruritus.

Follow-up (at 8, 7 and 4 months, respectively) was negative.

_Sarcoptes scabiei_ var. _hominis_ does not fly or jump: it crawls at the rate of 2.5 cm per minute on warm skin. A direct skin-to-skin contact lasting between 15 and 20 minutes is needed to transfer the mites from one person to another. The more parasites on a person, the greater the likelihood and speed of transmission, either direct or indirect. According to some authors, intercourses are a common transmission modality of the infestation among adults. In a study of risk factors for scabies in a sexually transmitted diseases unit, high-risk persons included men who have sex with men and men with sporadic sexual contacts. Scabies can be therefore considered as a true sexually transmitted disease. Scabies is less commonly transmitted by clothes, sheets and towels. Furthermore, living mites have been found on floors and furniture. In a study by Arlian _et al._, 44% of dust samples of infested patients’ homes contained mites, and 64% of these mites were living. Fomite transmission of the infestation is therefore considered to be possible. This modality of transmission is more frequent in crusted scabies. Some studies have documented survival of mites, at room temperature (21 °C) and 40-80% relative humidity, for more than three days. In particular, Arlian _et al._ demonstrated that high relative humidity values and low temperatures favored survival, whereas high temperatures and low relative humidity led to early death.

Transmission among family members and in institutional settings is common.

Predisposing factors are overcrowded places, poor environmental and personal hygiene, poor nutritional status, homelessness, severe psychiatric diseases. Transmission occurs by means of the gravid female, more rarely by means of larvae and nymphs. Latency time depends on mite burden and host immunity. It ranges between 3 weeks and 3 months: in most of the patients it ranges between 3 to 6 weeks. This is the latency time in patients infected for the first time: in reinfections, signs and symptoms arise after 1 to 5 days. This would mean that, although scabies does not induce a true definitive immunity, a certain degree of cell immunity occurs, possibly towards proteolytic and hydrolytic enzymes produced by females for the construction of the burrows and/or as a sensitization towards metabolic products released by mites during their growth or at their death and/or as a sensitization towards saliva and/or faeces.

The genetic predisposition for susceptibility or resistance to _Sarcoptes scabiei_ var. _hominis_ infestation has been hypothesized to be correlated with the dominance of an...
IgE-driven Th2 response in crusted (Norwegian) scabies or an interferon-g-dominated Th1 response that induces a mite control.12 In spite of a careful review of the international literature, we were not able to find reports of scabies acquired through massages. Therefore, we do think that this report is the first one about this topic. It is possible that in these patients scabies was transmitted by the sheets that covered the futon or by the towels used by the patients after the shower. It is unlikely that scabies has been transmitted by the oil used for the massage. As Chinese massage centers are proliferating (at least in Milan and its outskirts), we believe that cases of scabies caused by massages will be observed more frequently in the next future.

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References

Lymphedema and immunocompromised districts

TO THE EDITOR: Recent articles on angiosarcoma on the lower abdominal wall associated with chronic lymphedema1 and post-filarial cutaneous aspergillosis,2 as well as Stewart-Treves syndrome3 and giant angiofibromas in tu- neous infections, and immune disorders at sites of prior clinical events (as exemplified by chronic lymphedema in the first place, but also herpetic infection, vaccination, and heterogeneous physical injuries such as ionizing and ultraviolet radiation, thermal burns, and trauma), which selectively damage and immunologically alter the cutaneous site. In this light, Kacerovska et al.’s4 shrewd comment on the pendulous nature of the giant angiofibroma specimens, as indicative of localized lymphedema, directly points to considering the sites of onset of the giant lesions as immunocompromised mini-districts due to foci of microlymphedema. This view is supported by Paul and Carlson,5 who found that lymphangiectasias are common underlying warts and in normal peritumoral skin. In this regard, what is more demonstrative than the article by Shelley and Wood6 dealing with the transformation of the common
We are firmly convinced that a localized defect in immune surveillance as a result of chronic lymph stasis can lead to a series of pathologic events in lymphedematous districts or even micro-distincts, ranging from trivial angiectasias, through benign neoplasms such as verruciform xanthoma, to malignant ones such as Kaposi’s sarcoma, basal cell carcinoma, squamous cell carcinoma, melanoma and often invariably deadly angiosarcoma (Stewart-Treves syndrome).3,5

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References

TO THE EDITOR: A 35 year-old sales assistant in a jewelry store was responsible for selling silver articles. Her medical history did not include any relevant diseases or altered blood or urine values. Two years previously, a bluish pigment began to appear on the lunules of her fingernails (Figure 1). More recently, bilateral gray-blue blotches appeared on the gabella and in the naso-labial region (Figures 2, 3). Pigmented lesions of the conjunctiva and cornea were absent. An ultrasound scan of the liver did not reveal hyper-reflectivity. No other photo-exposed areas presented the bluish pigmentation, neither did the skin where covered by clothing or the mucosa. The patient had not taken any drugs, even topical, containing Ag+, had not undergone any unconventional therapies, and did not have tattoos. Her exposure to silver was solely occupational: she polished silver trays and frames every day. A skin biopsy confirmed the diagnosis by demonstrating brownish granules in the connective tissue surrounding sebaceous glands. Electron microscopy showed that the

Figure 1.—A bluish pigment on the lunule of fingernail.
patient was exposed through her occupation to both soluble Ag+ and metallic silver. She cleaned the silverware in a room behind the shop without gloves and only washed and dried her hands quickly when clients entered the shop; thus soluble Ag+ ions were released from the metallic silverware and absorbed by the skin through water or natural water/oil film. While the incidence of argyria is declining, its recognition remains important; pigmentation is permanent but benign. A few cases of occupational argyria have been published in Russia,3 while occupational corneal argyrosis most frequently affects silver solderers.4 Occupational silver intoxication is rare.2 Some cases have been reported in relation to wearing earrings, while iatrogenic cases due to silver sulfadiazine cream use, acupuncture and hemodialysis are increasing.5

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References
A controversial pigmented lesion located in the left subscapular region: a case of “collision” tumor

TO THE EDITOR: The association of contiguous or “collision” tumors in the same biopsy specimen is not uncommon although it is often reported in the literature. Most collision tumors occur by chance, and are not derived from similar cell lines and do not share pathogenic mechanisms. Some authors support the theory that there is a pathogenetic relationship between collision tumors themselves (especially seborrheic keratosis and melanocytic lesions); some others postulate that contiguous tumor represents only the presence of 2 or more common lesions juxtaposed by coincidence. Melanocytic nevus can occasionally be associated with several different tumor types. The most common association is with the basal cell carcinoma (BCC) and in some cases, it is very difficult to diagnose it clinically. Frequently, they are also reported the association with epidermoid cyst, trichilemmal cyst, steatocystoma, hidrocystoma and dermoid cyst, syringoma, trichoepithelioma and trichoadenoma. The association of a melanocytic nevus which arises countiguously with or adjacent to seborrheic keratosis is however uncommon and sometimes diagnosis can be a clinical challenge. We report an interesting case of composed pigmented melanocytic nevus associated with seborrheic keratosis.

A.G., 25 year-old, came to our attention because she noticed a change in color and size of a nevus located in the left subscapular region. This was present for some years and its image had been previously acquired through epiluminescence (Figure 1).

At the time of the visit, however, it was possible to appreciate a pigmented lesion that had the clinical demoscopic features of a seborrheic keratosis (Figure 2). After acquiring objective data conflicting with the anamnesis...
and the previous pictures, we decided to perform an excisional biopsy. The histological examination showed a pigmented compound melanocytic nevus associated with seborrheic keratoses (Figure 3). A symmetrical intradermal and junctional melanocytic proliferation composed of nests of melanocytes without atypia was reported. Above them there was a proliferation of pigmented small basoloid cells with uniform appearance with hyperkeratosis, acanthosis and pseudohorn cysts. These features led us to the diagnosis of composed pigmented melanocytic nevus associated with seborrheic keratosis.

This case is particular because a seborrheic keratosis in collision with a melanocytic nevus clinically appeared as one single lesion - the former one as an atypical spread of the latter one - that had rapidly developed. In such cases dermoscopy does not improve the diagnostic accuracy versus clinical examination.

In fact, even if the lesion presented the benign dermoscopic characteristics, according to the previous patient's pictures (which deposed for a major change of the melanocytic lesion), to the anamnesis and the possibility that melanoma may mimic a seborrheic keratosis, we have decided to perform the complete excision of the lesion. The histological examination clarified so that at the base of the change there was the formation of a pigmented seborrheic keratosis above the previously photographed melanocytic nevus.

The case confirms that preoperative diagnosis of cutaneous collision tumors remains extremely difficult, even with dermoscopy, especially when one of the lesions is melanocytic one. By performing a large incisional or an excisional biopsy, it will also be maximized the chance of identifying multiple lesions.

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