
Skin involvement and outcome measures in systemic autoimmune diseases

J. Albrecht¹, F. Atzeni², C. Baldini³, S. Bombardieri³, M.C. Dalakas⁴,
C. Demirkesen⁵, H. Yazici⁵, C. Mat⁵, V.P. Werth¹, P. Sarzi-Puttini²

¹Department of Dermatology, University of Pennsylvania, Philadelphia, USA; ²Rheumatology Unit, L Sacco Hospital University of Milan, Milan, Italy; ³Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy; ⁴National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, USA; ⁵Departments of Dermatology, Pathology and Internal Medicine, Cerrahpasa Medical Faculty, University of Istanbul, Istanbul, Turkey;

Please address correspondence to: Piercarlo Sarzi-Puttini, MD, Rheumatology Unit, L Sacco University Hospital, Via G.B. Grassi 74, 20157 Milan, Italy. E-mail: sarzi@tiscali.it

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ABSTRACT

This paper focuses on skin manifestations that can be observed in autoimmune diseases such as rheumatoid arthritis (RA), Sjögren syndrome (SS), dermatomyositis (DM) and Behçet syndrome (BS). In RA the most widely recognized skin lesion is the rheumatoid nodule. Other cutaneous manifestations can be observed either non-specific or related to the disease itself and/or to the commonly used drugs. Cutaneous manifestations are considered one of the most typical extraglandular features of primary SS, generally they are distinguished in vasculitic and non vasculitic lesions. Among non-vasculitic lesions, skin dryness (xerosis) has been shown to be very common in pSS while vasculitis lesions include typically flat and palpable purpura and urticarial vasculitis.

In DM the skin manifestations are also frequent and include a heliotrope rash (blue-purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (Gottron rash). The most frequent mucocutaneous finding in BS is aphthous stomatitis which can not usually be differentiated from idiopathic recurrent aphthous stomatitis on clinical grounds. The most typical skin manifestations are nodular lesions, which are commonly seen in BS and may be due to panniculitis [erythema nodosum (EN)-like lesions] or superficial thrombophlebitis.

Introduction

A variety of skin manifestations can be observed in autoimmune diseases such as rheumatoid arthritis (RA), Sjögren Syndrome (SS), dermatomyositis (DM) and Behçet syndrome (BS).

Rheumatoid arthritis and skin

Specific cutaneous manifestations of RA are varied and encompass a number

of entities, some of which define the dominant clinical features, such as the rheumatoid papule or subcutaneous cords, while others allude to the histopathology, i.e. rheumatoid neutrophilic dermatosis (RND) (1). Magro and Crowson (2) proposed a more simplified classification scheme using the adjectival modifiers of 'rheumatoid-associated' and then further categorizing the lesions according to the dominant reaction pattern. Three principal reaction patterns are recognized: (i) extravascular palisading granulomatous inflammation; (ii) interstitial and/or subcuticular neutrophilia; and (iii) active vasculopathy encompassing lymphocyte-dominant, neutrophil-rich, and granulomatous vasculitis. In most cases, an overlap of the three reaction patterns is seen.

Rheumatoid nodules. Rheumatoid nodules are the classic cutaneous manifestation of RA. They are not diagnostic for this disease and can be seen in other processes, especially other connective tissue diseases. Rheumatoid nodules occur in about 25% of patients with RA, and reflect high levels of disease activity and severity (4). Rheumatoid nodules are extremely relevant clinically as they correlate with more severe arthritis, higher levels of rheumatoid factor (RF), and with an increased incidence of rheumatoid vasculitis. The presence of RF within rheumatoid nodules suggests the possibility of immune complex-mediated vasculitis as the initiating event in rheumatoid nodule development (5). Clinically, they are firm, dome-shaped, skin-colored papules within the subcutaneous tissue. They are mobile and non-tender. Typically, they are present at pressure areas throughout the skin, like extensor areas of the forearm, finger joints, ischial and sacral prominences, occipital scalp, and Achilles tendon (1, 4, 5). Rheumatoid nodules are firm and frequently adherent to the underlining periosteum.

Rarely, they are the first presenting symptom of the disease and occasionally are present in internal organs; i.e. lungs, gallbladder, and heart. Histopathologically, the rheumatoid nodules manifest three characteristic zones (I) an inner central necrotic zone, (ii) a surrounding zone of palisading granulomas (predominantly macrophages), and (iii) an outer zone with perivascular infiltration of chronic inflammatory cells (4).

Cutaneous vasculitis (CV). CV, a complication seen in approximately 5% to 15% of patients with RA, is associated with positive, often high-titer RF anti-endothelial antibodies of IgA class, anti-Ro and anticardiolipin antibodies; advanced erosive disease; and increased patient morbidity and mortality (1, 4). CV should be suspected in advanced disease associated with fever, weight loss, and fatigue. CV can be present without active joint disease. Frequently, other extra-articular features are present like episcleritis, pleural, and pericardial effusions, a raised erythrocyte sedimentation rate (ESR), a low serum albumin, and sometimes liver enzymes disturbances (6). The most frequently observed features are chronic deep skin ulcers and nailfold lesions. The latter occur in about 5% of patients and are not associated with a worse prognosis. The clinical implication is that the primary joint inflammatory process is poorly controlled. Manifestations are often precipitated by abrupt discontinuation of systemic therapy with rebound circulating immune complex disease (6). CV can be classified by the size of the largest vessel involved and by the presence or absence of systemic involvement. The severity of the vasculitis cannot be defined by the cutaneous examination alone; a thorough evaluation searching for systemic involvement is essential. Jorizzo and Daniels (7) divided the rheumatoid vasculitis spectrum of disease in cutaneous vessels, ranging from severe with multisystem larger vessel vasculitis, to moderate with cutaneous small-vessel and possibly systemic small-vessel vasculitis, and mild with Bywaters lesions only.

Leg ulcers. Cutaneous ulceration, pri-

marily of the lower extremities, is frequently found in patients with chronic, debilitating disease (6). Lower extremity ulceration in patients with RA may be due to an associated disease process such as rheumatoid vasculitis or pyoderma gangrenosum (PG). If in CV the large vessels are affected, skin ulceration develops, often on lower extremities, or where skin is exposed to pressure, for example, interphalangeal joints of the toes, over bunions, ankles, elbows and, in bedridden patients, the buttocks. These ulcerations may be very painful, come in crops, and tend to grow and become chronic. Superinfection frequently occurs being particularly a great risk for patients with joint prostheses. In severe cases, ulcerations may form over subcutaneous nodules.

Neutrophilic dermatoses. The neutrophilic dermatoses are a group of related cutaneous disorders that frequently have systemic manifestations or associations (8). Several neutrophilic dermatoses occur in patients with RA. These include pyoderma gangrenosum, rheumatoid neutrophilic dermatosis, acute febrile neutrophilic dermatosis (Sweet's syndrome), erythema elevatum diutinum, subcorneal pustular dermatitis (Sneddon-Wilkinson's disease) and neutrophilic lobular panniculitis. Sweet syndrome is a reactive dermatological disease characterized by fever, leukocytosis, and tender, erythematous, well-demarcated papules and plaques, which show dense neutrophilic infiltrates and papillary dermal edema (8). It may occur in the absence of other diseases but is often associated with other systemic autoimmune diseases, infections and myelodysplastic malignancies. Its association with RA has been well described. Clinical overlap between these disorders led to the concept of "the neutrophilic dermatosis". In addition, patients with a neutrophilic skin disorder may also suffer from extra-cutaneous aseptically neutrophilic infiltrates. The mechanisms underlying the inappropriate activation of polymorphonuclears are poorly understood. Hematopoietic growth factors and adhesion molecules are believed to play a role in the pathophysiology of the neutrophilic dermatoses (8).

Adverse skin reactions to drugs

NSAIDs. The wide usage of non steroidal antiinflammatory drugs (NSAIDs) in RA patients raises the significance of their side effects. Among cutaneous symptoms intolerance was present at a relatively low frequency (9). The most frequent cutaneous side effects are caused by pyrazolon derivatives. Urticaria and angioedema were the most frequently observed symptoms.

DMARDs. Intramuscular gold is a well documented treatment in RA, but its mechanism of action is still poorly understood. Patients given gold salts have as high risk of cutaneous reactions. The mechanisms of cutaneous reactions are unknown and vary according to the molecules (1). Smokers, HLA Bw35 patients and perhaps atopic states are more prone to gold drug reaction. Inflammation at the site of injections is frequent but with no consequence (10). Pruritus is frequently observed, more often with oral salts. Exanthemas are common and may disclose an associated visceral disease. Drug hypersensitivity is rare, but severe. Accumulation (chrysiasis) may be observed with long-term treatment (10). Chrysiasis is a distinctive and permanent pigmentation of light-exposed skin resulting from the administration of parenteral gold salts. Focal aggregates of particulate gold are deposited in the reticular and papillary dermis in amounts that correlate with the degree of pigmentation (10). Characteristically, initially the periorbital region is affected by a mauve discoloration, which intensifies and deepens into a blue/slate-grey colour, while extending to involve the face, neck and upper limbs. Prevention is difficult, but measures to reduce sunlight exposure may be helpful. All these types necessitate drug interruption. Lichenoid eruptions require withdrawal, but the skin disease may continue.

Methotrexate (MTX) inhibits DNA synthesis by competition with dihydrofolate reductase. Adverse cutaneous reactions to MTX are usually dose-related and have been mainly reported in patients receiving extremely large doses of chemotherapy. Accelerated rheumatoid nodulosis, especially involving the hands and feet, has recently

been reported in patients receiving MTX therapy for RA and some cases have been reported for leflunomide (LEF).

Anti-TNF- α agents. Various adverse cutaneous reactions to anti-TNF- α monoclonal antibody have been reported (11). In clinical studies with infliximab adverse drug reactions were most frequently reported in the respiratory system and in the skin and appendages. Devos *et al.* (11) described 6 patients receiving anti-TNF- α therapy for Crohn's disease or RA who consulted the out-patient department for adverse cutaneous reactions: leukocytoclastic vasculitis, lichenoid drug reaction, pernio-like eruption, superficial granuloma annulare and acute folliculitis.

Anakinra. Anakinra, a recombinant-methionyl human IL-1Ra, has been shown to reduce joint inflammation and swelling, cartilage destruction, and bone resorption in several animal models of RA (12).

The only side effects that appeared to be closely linked with administration of anakinra were skin reactions at the injection site (12). Such reactions were the most frequent adverse events, and their frequency and severity increased with increasing doses of anakinra. Following adjustment for drug exposure time, the frequency of injection site reactions (ISRs) was 0.82 per patient-year of exposure in the placebo group (first 24 weeks) and 1.01, 2.43, and 3.73 for the 30 mg, 75 mg, and 150 mg doses of anakinra, respectively (long-term rates) (12). The most common symptoms and signs at the injection site were erythema, pruritus, and rash.

Mucocutaneous manifestations of Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder of unknown aetiology characterized by the dysfunction and destruction of exocrine glands (13). Cutaneous manifestations are considered one of the most typical extraglandular features of pSS and are generally distinguished in vasculitic and non-vasculitic lesions (13, 14). The number of literature studies specifically dedicated to skin involve-

ment, nonetheless, is quite limited and so far only few studies on large numbers of patients have been published (15-17). This appears quite surprising, considering the clinical significance of CV and its correlations with lymphoma development, but it is widely supposed that skin lesions might be overwhelmed by the most subjective mucosal impairment resulting from lymphocyte infiltration of salivary and lachrymal glands (13, 4, 18)

Cutaneous xerosis. Skin dryness has been shown to be a very common symptom in Sjögren's syndrome, with a frequency varying from 23% to 68% (13-15, 19). The level of xerosis is significantly higher in the primary than in the secondary form of the disease (17). The most classical subjective symptoms of xerosis are non-specific pruritus, sensation of dryness, and a 'pin prick-like' feeling, which are associated with various objective signs such as rough, inelastic, hypotrophic, or fine scaling skin (17). The mechanism responsible for the skin xerosis in pSS patients has not been adequately elucidated but an impairment of sweat glands is widely thought to be involved in pSS xerosis, since decreased sweating has been reported in pSS patients (14, 16). Other hypothesis mentioned an impairment of eccrine sweat glands in pSS, of cholinergic-stimulated flow and of sebaceous glands and apocrine glands abnormality (19).

Vascular lesions. Vascular lesions are quite frequent in pSS and their clinical manifestations are extremely various. Raynaud's phenomenon is probably the most common vascular feature seen in pSS with a prevalence varying from 15% to 35% (13, 17, 19). Moreover, it can be one of the earlier manifestations of the disease, preceding sicca symptoms by many years (13). CV include a variety of lesions depending on the level of blood vessel involvement in the skin and the intensity of inflammatory response. The most common vasculitic lesions are flat and palpable purpura (19). Flat purpura is usually seen in patients with hypergammaglobulinemia, while palpable purpura is a manifestation of dermal vasculitis (19). Purpura appears as recurrent crops of round,

pink, separated or confluent lesions turning dull purple and brown in a few days and finally resolving or leaving a pale brown stain (14); in contrast with simple purpura, palpable purpura does not blanch when pressure is applied to the skin. Moreover, due to the increased hydrostatic pressure, it typically involves lower extremity and buttocks (20). Cutaneous purpura has been associated with lymphoma development and mortality, CV thus becoming significant in the prognosis and outcome of patients with pSS (13, 21). Two different types of vasculitis have been histopathologically described in pSS: the neutrophilic inflammatory vascular disease, indistinguishable from a leukocytoclastic vasculitis, and the mononuclear inflammatory vascular disease (14, 19). The first pattern is characterised by an inflammatory infiltrate composed predominantly by neutrophils, many of which are fragmented. Moreover, the lesions typically display fibrinoid necrosis, lumen occlusion, and extravasation of red blood cells. The mononuclear inflammatory vascular disease is characterised by a mononuclear inflammatory infiltrate with invasion of the blood vessel walls. Fibrinoid necrosis is present, but less prominent than the neutrophilic inflammatory infiltrate (14, 19). Despite the evidence of these two forms of vasculitis, their clinical expression is very similar, so that is not predictable the histopathologic pattern of vascular insult in examining the skin (19). Nonetheless, neutrophilic inflammatory vascular disease, in contrast with mononuclear inflammatory vascular disease is statistically associated with antinuclear antibodies, high titres of anti-Ro/SSA and anti-La/SSB antibodies, hypergammaglobulinemia, RF and hypocomplementemia (14, 19).

The second most common form of inflammatory vascular disease is urticarial vasculitis, which in contrast with true urticaria is characterised by stinging or burning smaller lesions that usually persist for 24 hours and often resolve with hyperpigmentation, indicating red blood cell extravasation (20).

In addition to these manifestations, pSS patients may rarely demonstrate erythematous nodules on the lower extre-

mities, persistent plaque-like lesions (erythema multiforme-like lesions) as well as superficial ill-defined patches (erythema perstans) (14). In Japanese pSS patients annular erythema is often reported and it has been described as recurrent, non photosensitive, erythematous-indurated plaque-like lesion with central clearing without pigmentation or atrophy, typically involving the face, the upper extremities and the trunk (17).

Miscellaneous. A broad spectrum of other cutaneous manifestations has been described in pSS including angular cheilitis, eyelid dermatitis, vitiligo and alopecia (17). Angular cheilitis has been described as recurrent, symmetrical erythematous-squamous infiltrated lesion, often itching and fissuring and xerostomia may be a predisposing factor for its development (17). Eyelid dermatitis is defined by the presence of erythematous, infiltrated and lichenified lesions of the eyelids associated with itching and foreign body sensation. It has been hypothesized that ocular dermatosis may not be a simple consequence of contact sensitisation, but also the result of continuous rubbing of the periorbital area due to xerophthalmia (17). Alopecia areata has also been described in pSS as well as in other autoimmune diseases, and it has been explained by a possible lymphocytic infiltration of the sebaceous glands (19). Moreover, vitiligo consisting in localized areas of hypopigmentation has been associated with pSS too (14). Finally, a true complication of pSS is represented by malignant lymphomas (14, 21). Skin lymphomas are quite rare and data on their real incidence in pSS are lacking (17). Nonetheless, many case reports have been published describing cutaneous B cell lymphomas, or most infrequently T cell lymphomas, and all these cases have to be considered as part of the increased risk of pSS proliferative disorders (21, 22).

Dermatomyositis

Dermatomyositis (DM) is one of the three main inflammatory myopathies, the other two being polymyositis and inclusion-body myositis (23). Before the extensive use of immunosuppres-

sive drugs, DM was the cause of considerable disability and mortality, especially in children. During the last 30 years, the extensive use of these drugs and the better understanding of the immunopathology of the disease have significantly improved the prognosis. DM, a disease affecting skin and muscle, is cared for not only by neurologists but also by rheumatologists and dermatologists.

Clinical manifestations. DM occurs in both children and adults. It is a distinct clinical entity identified by a characteristic rash accompanying or, more often, preceding the muscle weakness. The skin manifestations include a heliotrope rash (blue-purple discoloration) on the upper eyelids with edema, a flat red rash on the face and upper trunk, and erythema of the knuckles with a raised violaceous scaly eruption (Gottron rash) (23-25). The initial erythematous lesions may result in scaling of the skin accompanied by pigmentation and depigmentation, giving at times a shiny appearance. In contrast to systemic lupus erythematosus (SLE), in which the phalanges are involved and the knuckles are spared, the erythema of DM spares the phalanges. The erythematous rash can also occur on other body surfaces, including the knees, elbows, malleoli, neck and anterior chest (often in a V sign), or back and shoulders (shawl sign), and may be exacerbated after exposure to the sun. Dilated capillary loops at the base of the fingernails are also characteristic of DM. The cuticles may be irregular, thickened, and distorted, and the lateral and palmar areas of the fingers may become rough and cracked, with irregular, "dirty" horizontal lines, resembling a mechanic's hands. DM in children resembles the adult disease, except for more frequent extramuscular manifestations, as discussed later. A tiptoe gait due to flexion contracture of the ankles is a common early abnormality in children. A common early abnormality in children is "misery," defined as an irritable child that feels uncomfortable, has a red flush on the face, is fatigued, does not feel like socializing, and has a varying degree of muscle weakness (24-28). When the weakness develops, it

takes the form of a myopathy, with proximal more than distal involvement. The degree of weakness can be mild, moderate, or severe, leading to quadriplegia. Some patients with the classic skin lesions appear to have clinically normal strength even up to 3 to 5 years after onset. This form, referred to as "dermatomyositis sine myositis" or "amyopathic dermatomyositis", has a better overall prognosis (29). Although in these cases the disease appears limited to the skin, the muscle biopsy shows significant perivascular and perimysial inflammation and immunopathological features identical to those seen in classic dermatomyositis suggesting that amyopathic and myopathic forms are part of the range of DM affecting skin and muscle to a varying degree.

DM usually occurs alone, but it may overlap with systemic sclerosis and mixed connective tissue disease. Fasciitis and skin changes similar to those found in dermatomyositis have occurred in patients with the eosinophilia-myalgia syndrome associated with the ingestion of contaminated L-tryptophan (24); and with eosinophilic fasciitis or macrophagic myofasciitis (30).

Extramuscular manifestations. In addition to the primary disturbance of the skeletal muscles and skin, extramuscular manifestations may be prominent in some patients with dermatomyositis. These include (a) dysphagia, similar to that of patients with scleroderma; (b) cardiac abnormalities consisting of atrioventricular conduction defects, tachyarrhythmia, low ejection fraction, and dilated cardiomyopathy (either due to the disease itself or, more often, to hypertension or fluid retention associated with long-term steroid use); (c) pulmonary involvement, resulting from primary weakness of the thoracic muscles, drug-induced pneumonitis (e.g., from methotrexate), or interstitial lung disease. Interstitial lung disease may precede the myopathy or occur early in the course of the disease, especially in patients who have anti-Jo-1 antibodies, as discussed later; (d) subcutaneous calcifications, sometimes opening onto the skin and causing ulcerations and infections, especially in children (28); (e) gastrointestinal ulcerations, seen more

often in the childhood form, due to vasculitis and infections; (f) contractures of the joints, especially in the childhood form; and (g) general systemic disturbances, such as fever, malaise, weight loss, arthralgia, and Raynaud phenomenon, especially when dermatomyositis is associated with a connective tissue disorder.

Diagnostic investigations. The clinical diagnosis of DM is confirmed by assessing the level of serum muscle enzymes, the electromyographic findings, and the muscle biopsy. In classic cases, however, the typical skin manifestations in combination with muscle weakness are almost sure indicators of dermatomyositis, even on clinical grounds alone.

Electromyography. Needle electromyography shows myopathic potentials characterized by short-duration, low-amplitude polyphasic units on voluntary activation and increased spontaneous activity with fibrillations, complex repetitive discharges, and positive sharp waves. Mixed myopathic and neurogenic potentials (polyphasic units of short and long duration) can occasionally be seen in DM as a consequence of muscle fiber regeneration and indicate chronicity of the disease.

Muscle biopsy. Muscle biopsy is the definitive test to exclude other neuromuscular diseases and assess severity of involvement. The following unique histological features are characteristic of DM; a) endomysial inflammation, predominantly perivascular or in the interfascicular septa and around rather than within the fascicles; b) endothelial hyperplasia with tubuloreticular profiles in the intramuscular blood vessels along with fibrin thrombi (especially in children) and obliteration of capillaries; c) necrosis, degeneration, and phagocytosis affecting often groups of fibers within a muscle fascicle in a wedge-like shape or at the periphery of the fascicle due to microinfarcts within the muscle; and d) perifascicular atrophy (28). The presence of perifascicular atrophy is diagnostic of dermatomyositis, even in the absence of inflammation. The skin biopsy also shows the abnormalities mentioned earlier but taking routine skin biopsy samples is not helpful (31).

Treatment. The evidence that immunopathologic mechanisms are primarily involved in the pathogenesis of DM justifies treating the disease with immunosuppressive therapies. The goal of therapy in DM is to improve function in activities of daily living as the result of improvement in muscle strength, and improve the skin alterations. Although improvement in strength is usually accompanied by a fall in serum creatine kinase, decreases of serum creatine kinase have to be interpreted with caution because most immunosuppressive therapies result in a decrease in serum muscle enzymes without necessarily improving muscle strength (23). For patients with disease limited to the skin, our preference is to use low doses of steroids or hydroxychloroquine sulfate and avoid immunosuppressants until weakness develops (32).

In case of severe disease according to the efficacy of the aforementioned agents and our experience, our step by step approach in the treatment of DM is as follows (25, 32):

Step 1: High-dose prednisone (oral or intermittent intravenously in acute cases)

Step 2: Add mild immunosuppressants, such as azathioprine, methotrexate or mycophenolate, for a steroid sparing effect

Step 3: If Step 1 fails, try high-dose intravenous immunoglobulin

Step 4: If the above fail, consider a trial, with guarded optimism, of one of the following agents, chosen according to the patient's age, degree of disability, tolerance, experience with the drug and the patient's general health: cyclosporin, cyclophosphamide, Tacrolimus or Rituximab.

Treatment for calcinosis remains difficult. Attempts with alendronate, probenecid, or diltiazem thought to be promising, offer limited help (33, 34).

Behçet syndrome: Skin-mucosa manifestations

The most frequent finding in Behçet syndrome (BS) is aphthous stomatitis which can not usually be differentiated from idiopathic recurrent aphthous stomatitis on clinical grounds. In a prospective, cross sectional study among

202 patients attending a dedicated clinic 40 % of BS patients had active oral ulcers with more severe disease among women (35). We find this observation quite useful especially in designing drug studies.

Nodular lesions seen in BS may be due to panniculitis (erythema nodosum like lesions) or superficial thrombophlebitis. It can be difficult to tell one from the clinically. Cutaneous ultrasound might be helpful in differential diagnosis.

EN like lesions are characterized by neutrophil-predominating infiltrate both in lobules and septum of the subcutis. Rarely, the inflammatory cell infiltrate is composed mainly of lymphocytes. Neutrophilic vasculitis – not seen in idiopathic EN due to other causes – involving mostly arterioles and venules, can be detected in almost half of the cases.

Genital ulcers are one of the cardinal signs of BS with a frequency of about 85%. They usually begin as a papule, pustule or necrotic crust that ulcerate in a short period of time. Genital ulcers of BS can be painful. Their borders are regular and oedematous and their base are covered with a yellow fibrin. They are oval or round with punched-out appearance. In a recent prospective study we showed that not infected genital ulcers usually healed in 10 to 30 days (36). In males, genital ulcers occur mostly on scrotum (89%), penis, femoral and perianal regions. Large ulcers (> 1 cm) ended up with scarring also in 89% of the lesions while the scarring rate of smaller ulcers was 49%. In females, ulcers are commonly found on both major and minor labiae. Vaginal and cervical lesions are less frequent. Similarly large ulcers healed with scar, while only 54% of the small ulcers did so in females. The ulcers that were located at labia minor did not result in scarring rather similar to the situation in oral ulcers. It is also possible that mucosal scarring can not be discerned by the naked eye. Genital scarring is usually good evidence of BS in a patient suspected of having the syndrome.

The pathogenesis still remains unknown. It might be that several patho-

genetic mechanisms might be operative. By factor analysis among 272 consecutive patients we have shown that acne lesions of BS go together with arthritis while big vessel disease is associated with superficial thrombophlebitis (37). The acne–arthritis association has previously and separately been reported on by our group in another controlled study among a different group of patients (38).

We now know that the acne lesions, as well as the pathergy lesion (unpublished observations) of BS patients are not sterile and a decreased tPA response seems to be primary marker for acute thrombosis in BS (39, 40). These findings, to us, suggest that there might indeed be more than one pathogenetic mechanism or trigger in a susceptible host in, perhaps justifying the use of syndrome rather than disease for this entity.

We recently surveyed the two decade mortality and morbidity of BS and saw that the disease activity was usually confined to the early years of disease course. This was particularly true for skin-mucosa disease (41). When one one took those patients with mainly skin-mucosa disease at the onset and reexamined them 20 years later many would not fulfill any one of the classification criteria proposed.

Oral ulcerations (OU) are the main features of Behçet's Syndrome (BS) and decrease the life quality. In an open study the efficacy of *Lactobacillus brevis* lozanges in oral ulcer was studied among 25 consecutive patients with BS in a pilot protocol. A significant reduction in the numbers of oral ulcer OU at end of one week treatment was found. In this pilot and open study *Lactobacillus brevis* lozanges seemed to be rather effective in controlling the oral ulcers of BS (42).

Tumor necrosis factor-alpha blockers, as potent inhibitors of inflammation, are finding increasing use in BS like in many other diseases. We recently published a placebo controlled double-blind study to determine the efficacy of the tumor necrosis factor-alpha blocker etanercept for pathergy and monosodium urate (MSU) induced inflammation and on the mucocutaneous and articular manifestations in BS patients. This

trial show that etanercept at 25 mg twice a day for 4 weeks is more effective than placebo in the treatment of mucocutaneous manifestations, especially the oral ulcers, however, etanercept did not effect the pathergy reaction and the cutaneous response to MSU crystals (43).

Finally although steroids are widely used in BS their efficacy has never been formally tested. To this end we studied the efficacy of depot steroid (40 mg methyl prednisolon acetate) intramuscular injections for the treatment of mucocutaneous manifestation of in 86 BS patients in double-blind placebo controlled study. Low dose depot-steroids use in BS, useful in controlling erythema nodosum lesions among females, however it is ineffective for oral ulcerations, genital ulcers, folliculitis and arthritis during the trial (44).

Outcome measures in skin manifestations

Comparative trials depend on outcome instruments that measure the extent and severity of a disease and can be used to compare the baseline status with the condition of the disease after treatment has been initiated. Unfortunately to date the number of outcome instruments available to study autoimmune diseases is quite limited.

The measure of extent of body surface area involved is inappropriately crude for diseases like acne – or indeed DM or cutaneous lupus erythematosus (CLE) (45). These diseases may hugely affect patients' life, while they only affect small percentages of body surface area (45). Autoimmune diseases, particularly systemic lupus erythematosus (SLE) and DM, can lead to functional disability due to systemic involvement or muscle disease, even though the skin lesions are improving on treatment, thus blurring or obstructing the treatment effect. The desirable qualities of an outcome instrument for clinical trials have been summarized very succinctly by Finlay (46). Unfortunately most of the developed scores in dermatology are disease specific and many have not been properly evaluated.

For both DM or CLE, development of the cutaneous outcome instruments is a

fairly recent development and experience with these instruments is limited. However, in addition to these instruments, associated symptoms like itch, pain, or fatigue should be measured as well. This should be done in a separate score because a combined score that reflects patient and physician assessment may be quite hard to interpret and it is unclear how the different aspects of the disease should be weighed (47, 48).

Often the general criticism is voiced that outcome instruments do not adequately reflect the improvement of the patients. However, a disease experience is a not a linear process that can be summarised in any score, e.g. a very small PASI score can be severely disabling if psoriasis affects the hands of a surgeon.

Outcome measures in dermatomyositis. As a frequently photosensitive disorder, cutaneous DM typically affects exposed areas of skin on the face and upper extremities. The availability of validated outcome measures of DM skin disease activity could be of considerable benefit in clinical trials of new therapeutic agents.

The Dermatomyositis Skin Severity Index (DSSI) has been closely modeled on the Psoriasis Activity Score Index (PASI), which to date is the most successful and the dominant outcome instrument for psoriasis (49). The basis for the practically identical design of the DSSI and the PASI is the clinical observation that the skin lesions of both diseases share characteristics that are measured by the PASI.

The PASI is a clinical scoring system based on the visual inspection of four main body areas, which are the head, the trunk, the upper extremities, and the lower extremities. The observer estimates the percentage of skin that is affected by the disease in each area. The PASI and the DSSI then score each affected area according to the average redness, induration and scaliness of the lesions in the respective areas.

Through a very thorough evaluation process the DSSI has demonstrated content validity, construct and criterion validity as well as inter-rater and intra-rater reliability in two academic cen-

ters. After its publication it will be a useful instrument for clinical research of the skin manifestations of DM.

Outcome measures in cutaneous lupus erythematosus. In epidemiological studies, skin involvement has been found to be the second or most common manifestation and second most frequent presenting manifestation of SLE (50). Some types of cutaneous LE lesions such as classical discoid LE (DLE) and subacute cutaneous LE (SCLE) can occur in individuals who develop only minor manifestations of SLE or never develop any degree of SLE at all.

According to an FDA background paper, measures of clinical responses to therapy are currently lacking many elements or their validation is so low-level that their suitability for clinical trials is doubtful (47). The FDA assessment of the available scores to measure SLE was that while they acknowledge skin involvement as one aspect of the global score, these instruments are not sufficient to allow meaningful assessment of therapeutic effectiveness.

Recently, an instrument, the Cutaneous LE Activity and Severity Index (CLASI), was designed and partially validated. This index is being used in a number of clinical trials and should allow comparisons of the therapeutic success between trials.

The CLASI, the PASI, the DSSI and many other clinical instruments depend heavily on the assessment of erythema when activity of the diseases is measured. This is quite reasonable since erythema is a prominent symptom that is easily recognized by patients and physicians alike.

For the CLASI we have chosen to describe the extent of disease in terms of areas instead of percentage of body surface area or number of lesions. This choice was based on the experiences with other scores like the SCORing Atopic Dermatitis (SCORAD) that heavily depend on assessment of the percentage diseased skin surface area. Repeatedly this assessment has been shown to be hard to reproduce (51-53). LE affects certain areas of the body more than others, since the disease develops primarily in photosensitive and thus visible areas. Discoid LE, for ex-

ample, quite often only affects the head but can be severely disfiguring and arguably more serious than SCLE, which may fade without scarring. The detailed description of the face and the scalp leads to an increase in weight assigned to the head, reflecting the patients' experience.

The differentiation between activity and damage in our scores is unusual for dermatological scores, however this distinction is established for scores of SLE, where these aspects are commonly separated. Activity and damage are distinct aspects of the disease and the damage depends largely on the form of cutaneous LE present. We have chosen to calculate the score for activity and damage separately, assuring that the CLASI is more reactive to therapy-induced changes of activity. In contrast, using one summary score may lead to paradoxically stable scores as the activity decreases and the damage becomes apparent. Thus the score may remain the same, while the clinical picture changes completely.

The CLASI is designed as a table where the rows denote anatomical areas, while the columns score major clinical symptoms. The left side of the instrument describes the activity of the disease while the right side describes the damage done by the disease. Activity is scored as a summary score of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss and non-scarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. Patients are asked whether dyspigmentation due to CLE lesions usually remains visible for more than 12 months, which is taken to be permanent. If so, the dyspigmentation score is doubled. The scores are calculated by simple addition based on the extent of the symptoms. The extent of involvement for each of the skin symptoms is documented according to specific anatomic areas that are scored according to the worst affected lesion within that area for each symptom. The subjective symptoms documented by the patient like itch, pain and fatigue are recorded separately on a visual 1 to 10 analogue scales. These symptoms can be impor-

tant for the assessment of therapeutic success because they can be more reactive than the visual skin to therapeutic improvement.

The validation of the CLASI is described in detail elsewhere (54). This process has confirmed content validity. Construct validity is assessed by comparing the instrument to the other outcome instruments for cutaneous LE. These do not exist, but the measures used in the SLE instruments available correlate with the CLASI. We did not assess criterion validity because the reason for the development of the instrument was that there was no measurement available. Reliability studies demonstrated excellent inter-rater and intra-rater reliability. Currently we are conducting a clinical study to demonstrate clinical responsiveness of the CLASI on 12 patients who are started on new treatment. Preliminary analysis of the first half of the patients shows that the CLASI reflects treatment success and demonstrates clinical responsiveness, but remains unchanged if the treatment fails.

The development of two skin specific outcome instruments for autoimmune diseases within one year is an important step forward. The experience with SLE illustrates that a large community can develop a variety of instruments. This abundance makes the comparison of clinical trials more difficult and limits the experience with each instrument. To avoid this, an open and interactive development process is needed.

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