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Sclerodermalike syndromes: The great imitator

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Abstract Sclerodermalike syndromes (SLSs) comprise diseases with mucin deposition (eg, scleromyxedema, scleredema), with eosinophilia (eg, eosinophilic fasciitis), metabolic or biochemical abnormalities (eg, nephrogenic systemic fibrosis), or endocrine disorders (eg, POEMS syndrome, or polyneuropathy, organomegaly, endocrinopathy, monoclonal lymphoproliferative disorder, and hypothyroidism). Chronic graft-versus-host disease may also show sclerodermalike skin changes. Inherited progeria syndromes with early aging (eg, Werner syndrome) and a heterogeneous group of hereditary disorders with either skin thickening (eg, stiff skin syndrome) or atrophy and tightening (eg, acrogeria) can also imitate classic systemic sclerosis (SSc). In addition, SLSs can be provoked by several drugs, chemicals, or even physical injury (eg, trauma, vibration stress, radiation). In SLSs, the distribution of skin involvement seems to be atypical compared with SSc. The acral skin involvement is usually missing, and lack of Raynaud phenomenon, scleroderma-specific antinuclear antibodies, the absence of scleroderma capillary pattern, and internal organ manifestations indicate the presence of an SLS. Skin involvement is sometimes nodular, and the underlying tissues can also be affected. For the differential diagnosis, a skin biopsy of the deeper layers including fascia and muscle is required. Histology does not always allow differentiation between SSc and SLSs; therefore, the diagnosis is often based on the distribution, quality of cutaneous involvement, and other accompanying clinical features.

Introduction

Systemic sclerosis (SSc) is characterized by vascular abnormalities, fibrosis, inflammatory changes, and late stage tissue atrophy. The pathology of SSc is complex and includes as a hallmark of disease skin fibrosis called scleroderma.[1] The distribution of the skin involvement in SSc is very characteristic, and the acral regions including the digits are almost always involved.[2,3] Skin thickness is caused by increased collagen and intercellular matrix formation in the dermis and by edema probably caused by both microvascular injury and some inflammation. With the accumulation of collagen and fluid, the skin becomes thickened, making it impossible to pinch it into a normal skin fold. In the next indurative phase, the skin also becomes shiny, taut, and adherent to the subcutis, whereas in the late stage, the skin appears thin, atrophic, and often tightly tethered to the underlying tissue.

Apart from the characteristic skin fibrosis, additional clinical manifestations are also suggestive of SSc. Raynaud phenomenon is present in almost all patients with SSc, although it may be missing in some early diffuse SSc cases at disease

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onset.[2] Another hallmark of SSc is the presence of scleroderma-specific antinuclear antibodies (anticentromere, anti–topoisomerase 1, anti–RNA polymerase III). Patients with SSc usually exhibit characteristic nailfold capillaroscopy findings, including capillary dropout and giant capillaries.[4] Scleroderma nailfold capillary pattern is present in approximately 90% of the SSc cases.[2] In the majority of patients, fibrosis, vasculopathy, and inflammation also lead to typical organ manifestations, including interstitial lung disease, pulmonary hypertension, scleroderma renal crisis, heart involvement, digital ulcers, synovitis, and variable gastrointestinal involvements, which define the prognosis of the disease.[2,5]

Sclerodermalike syndromes (SLSs) mimic idiopathic SSc, because they exhibit skin findings that include either the classic early skin thickening or late skin tethering and atrophy present in SSc.[6–13] Several important signs may also indicate that the patient does not have SSc, but rather another SSc-like disorder. The lack of Raynaud phenomenon, a negative screening test for antinuclear antibodies, or the absence of scleroderma pattern on nailfold videocapillaroscopy may be a valuable indicator of the presence of a sclerodermalike disease. Lack of typical internal organ manifestations may also indicate the presence of a sclerodermalike disorder. The skin involvement in SLSs tends to begin superficially and progresses into the deep tissues, often affecting the deeper layers including subcutaneous tissue and fascia.

The nature, quality, and distribution of skin involvement are pivotal elements in the differential diagnosis of these particular disorders (Figure 1). The presence of musculoskeletal involvement and organ involvement is also crucial in the distinction of idiopathic scleroderma that forms from sclerodermalike diseases. A biopsy, involving deep skin layers, fascia, and even muscle, is almost mandatory for the differential diagnosis.

SLSs with mucin deposition

Scleromyxedema

Scleromyxedema is an orphan disease[14] which belongs to the inflammatory mucinoses. It is often associated with other diseases including hematologic malignancies,[15] hepatitis C, or HIV infection[16,17] and with connective tissue disorders[18,19] including scleroderma.[20] The affected patients are middle aged without any sex or race predominance.[21] Scleromyxedema is characterized by waxy indurated papules with marked skin sclerosis and induration.[21–23] Initially clusters of papules and diffuse plaques appear symmetrically on the face, neck, upper part of the trunk, forearms, and hands. These particular eruptions may be erythematous or hyperpigmented. As the disease progresses, a diffuse, symmetric skin involvement appears. The presence of diffuse, waxy papules in linear arrays and in a characteristic distribution that includes the glabella and posterior auricular area are the leading clinical manifestations of scleromyxedema.[14] The extensive facial mucin deposition and involvement of the glabella may cause an appearance of the so-called leonine face.[24] The deep furrowing is also classically

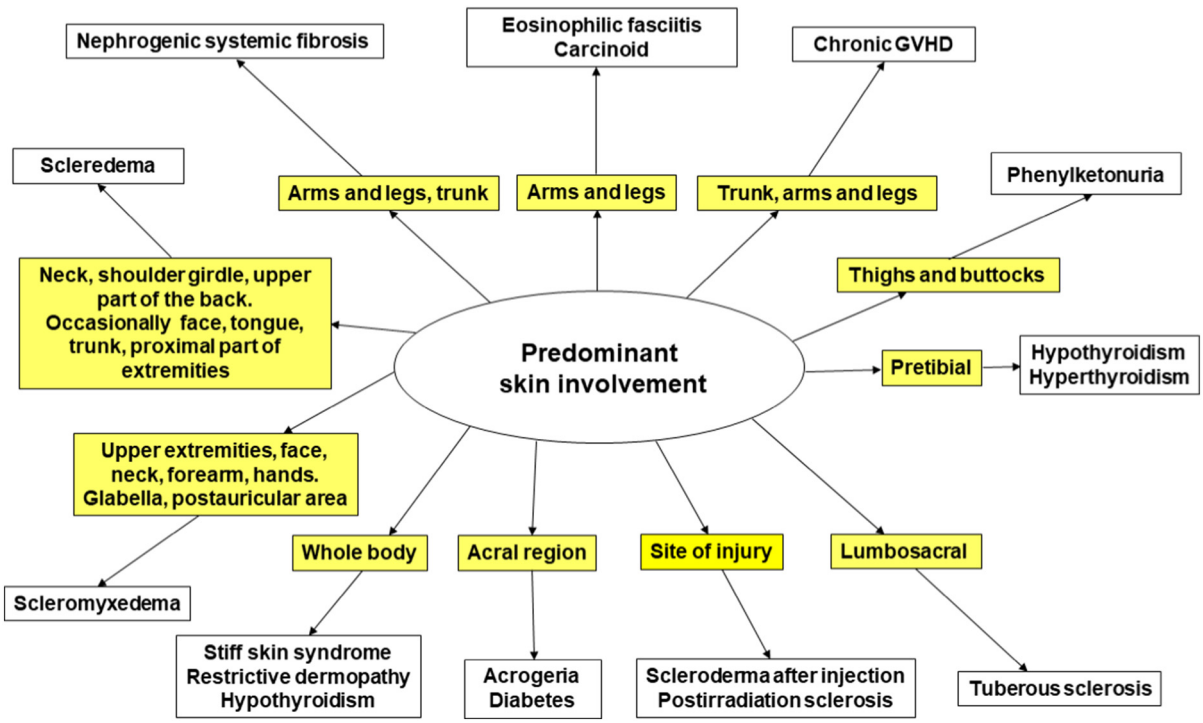

Fig. 1 Predilection sites of skin involvement in sclerodermalike syndromes. Reproduced with permission from L. Czirják.

palpable on the trunk and extremities, being known as the "Shar-Pei sign."[21] The palms, scalp, and mucous membranes are spared.

Myopathy of the proximal muscles, esophageal dysmotility, polyarthritis, pulmonary involvement, central and peripheral nervous system clinical manifestations, and rarely Raynaud phenomenon, may also occur.[21,25,26] Cases with severe acute central nervous system syndrome and encephalopathy have been reported many times.[27,28] The disease course in most of the cases is progressive,[21] and a lethal course has been also described.[29,30]

Monoclonality in the serum is a common finding,[31–36] which is predominantly immunoglobulin G (IgG), lambda type.[15,37] Occasionally, IgG kappa, IgM lambda, or IgA lambda and kappa types may be present.[38,39] There can be both improvement and remission both in monoclonality and clinical findings in a patient after an autologous stem cell transplantation, perhaps indicating a potential causative role of paraproteinemia in skin clinical manifestations and other organ manifestations.[40] The paraprotein levels may not correlate with the severity or progression of the disease or the response to treatment in a multicenter study.[21]

With regard to pathogenesis, it is very likely that the fibroblasts are active and produce large amounts of mucin.[41,42] It is also widely accepted that the circulating cytokines (tumor necrosis factor alfa, transforming growth factor beta, and interleukin [IL] 1) may also play a role in the pathogenesis of scleromyxedema. These are proinflammatory cytokines and have a stimulatory effect on fibroblasts to produce glycosaminoglycans,[21] but the direct evidence is very limited.[27,43]

The typical histopathologic findings in the skin include mucin deposition (mainly hyaluronic acid in the upper and middle region of the dermis), fibrosis (thickened collagen bundles and wide intercollagenous spaces), and fibroblast proliferation.[14,44,45] The loss of elastic fibers is also very typical.[14] Mucin deposition may also be detectable in other internal organs including the heart, lung, kidney, and lymph nodes.[29,46,47] In nearly one fifth of patients, histopathologic examination shows typical granuloma annularelike findings with superficial perivascular infiltration of T lymphocytes and interstitial proliferation of CD68 epithelioid cells.[14]

The disease is often refractory to therapy.[21,48] High-dose intravenous immunoglobulin (IVIG) has been used with good results by several groups; however, long-term maintenance therapy seems to be necessary.[26,49,50] Discontinuation of IVIG therapy frequently has led to a slow relapse in skin lesions,[21] although the improvement in the skin manifestations might be long-standing.[50] Currently, IVIG seems to be the first-line therapy; however, for extracutaneous manifestations or for maintenance treatment, a combination or sequential treatment (IVIG plus thalidomide) is also a reasonable choice in therapy resistant cases.[51] Autologous stem cell transplantation is a promising approach for the treatment of severe and relapsing cases[40,52]; however, in persistent cases with more than 3 years of disease duration, a complete remission has been observed in only 10% of patients.[53]

Scleroderma adultorum of Buschke

Scleroderma adultorum of Buschke is characterized by firm, nonpitting edema that typically begins at the neck and spreads to the back, shoulders, and face (Figure 2). The hands and feet are characteristically spared.[12,23] Scleredema has also been described in association with various infections, paraproteinemia, or diabetes mellitus[54]; however, scleredema may also be idiopathic.[55]

Type 1 scleredema is an acute disease usually developing a few weeks after a bacterial or a viral respiratory infection, mainly in childhood, and completely resolves within a few months to 2 years.[23,56] Skin involvement develops quickly on the neck, then symmetrically spreads distally to the whole trunk and around the shoulders. About 60% of this type of scleredema is triggered by *Streptococcal* infections, with elevated anti–streptolysin O titer in the serum, and mild anemia. One pathogenetic hypothesis suggests that scleredema may develop due to direct actions of bacterial toxins and adrenal steroids released in response to the infection.[56,205] Ultrasonography examination with a high-frequency linear array transducer of 12.0 to 15.0 MHz is able to identify the thickened skin in a prone position, owing to the anatomic location

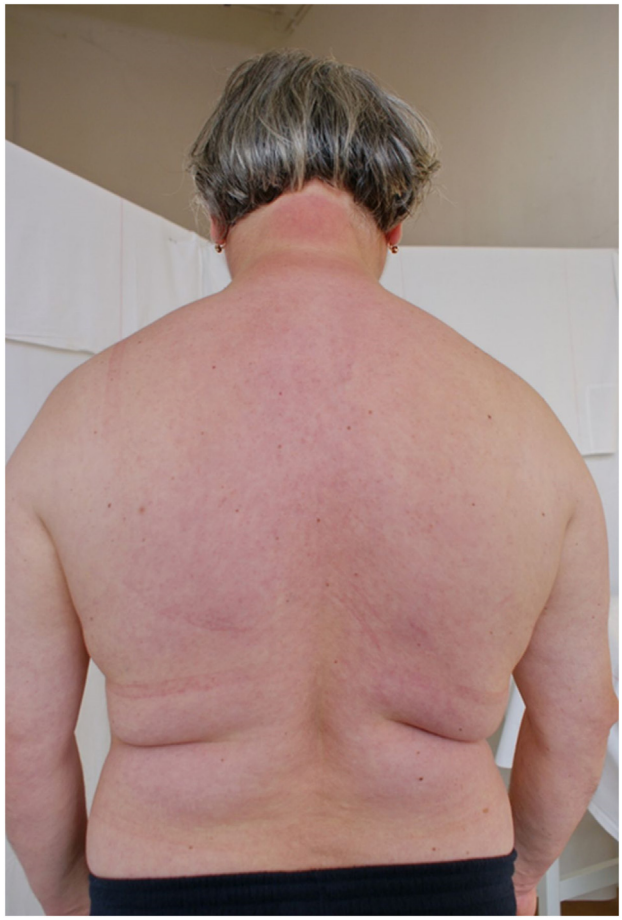

Fig. 2 Skin involvement on the neck and trunk in scleredema adultorum of Buschke.

of the lesions.[57] A skin biopsy may reveal, on staining, IgG, IgM, and C3 deposits at the dermal-epidermal junction.

The second main type of scleredema adultorum follows a slow and rather progressive course, without a history of a preceding disease. Two to 10 years later, this type of scleredema often is associated with monoclonal gammopathy, multiple myeloma, or amyloidosis. In this subgroup, IgG and IgA type monoclonal gammopathies are frequently found.[57–59]

Type three scleredema usually develops in patients with diabetes mellitus (2.5% to 14% of patients with diabetes), the majority of whom are obese and have untreated disease.[60,61] An insidious onset is characteristic for this particular subset. A relatively high prevalence of coexisting thyroid disorders, especially hypothyroidism, can be also found. As to the pathogenesis of scleredema diabeticorum, advanced glycation end-products have been suggested as causing collagen fibers to become resistant to breakdown.[1,62]

The biopsy specimens show normal epidermis with thickened dermis containing mucopolysaccharides (mainly mucin) in the spaces between large, swollen collagen bundles. The subcutaneous fat tissue also contains collagen fibers.[56]

Therapeutic options for patients with severe, widespread scleredema may include phototherapy (psoralen and ultraviolet A [PUVA], PUVA-bath, ultraviolet B, UVA1), physical therapy (eg, frequency-modulated electromagnetic neural stimulation), and different medications (methotrexate, glucocorticoids, cyclosporine, prostaglandin E1, intravenous immunoglobulin). Similar to other sclerodermalike diseases, evidence-based recommendations for the treatment of scleredema adultorum are still missing.[23,55,59–61,63,64] Strict control of diabetes also seems to be useful in the treatment.[63] Recently tranilast, a newly developed antifibrotic agent suppressing transforming growth factor beta–induced type I collagen synthesis in human dermal fibroblasts,[65] has been suggested for the treatment of scleredema.[64]

SLSs in endocrine and metabolic abnormalities

POEMS syndrome

POEMS syndrome (Crow-Fukase syndrome) is characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, including local-to-generalized hyperpigmentation and sclerodermalike skin findings.[66–70] POEMS syndrome shows a predominance of 63% for men and the onset of disease is in the sixth decade.[71] The diagnostic hallmark with rare exceptions[72] is a subacute peripheral demyelinating neuropathy,[73] triggered by plasma cell dyscrasia.[74–76] Skin findings are frequently present (90% to 100%)[77] with the most common findings being hyperpigmentation and hemangioma (approximately 50%)[78] followed by hypertrichosis[79] and vascular skin changes. A definitive diagnosis of Raynaud phenomenon was found in only 20% of patients. Skin thickening is also present in more than half of the patients[69]; however, the involvement of fingers (mimicking sclerodactyly) was found in only 16% of cases.[80] Other skin findings include facial lipoatrophy, infiltrated livedo reticularis, necrosis, acrocyanosis, flushing, rubor, nail changes (leukonychia and clubbing), and calciphylaxis.[78,81]

Additional clinical features of POEMS syndrome include sclerotic bone lesions, Castleman disease, papilledema, pleural effusion, edema, ascites, endocrinopathy, organomegaly, weight loss, hyperhidrosis, pulmonary hypertension, diarrhea, and altered laboratory parameters including elevated vascular endothelial growth factor (VEGF), monoclonality, low vitamin B_{12} level, and thrombocytosis or polycythemia.[75,77,82]

Approximately two thirds of patients have at least one endocrine abnormality at presentation, but endocrinopathies can develop also during the course of the disease.[83] The most frequent endocrinopathies in decreasing order are hypogonadism, hypothyroidism, abnormalities of the adrenal-pituitary axis, diabetes mellitus, and parathyroid hormone elevation.[83] Due to the high prevalence in the general population, diabetes mellitus and hypothyroidism are not considered to be sufficient to fulfill the minor criteria for the diagnosis of POEMS syndrome.

Regarding monoclonality, protein electrophoresis is positive only in half of the cases, however, the immunofixation shows positive result in up to 90% of patients.[84] Histopathologic examination shows hyperpigmentation of the basal layer, inflammatory infiltrates, and dermal fibrosis. In a French study, among the eight samples from seven patients with skin thickening, only three showed a slight sclerosis of the dermis with vascular hyperplasia.[79] Diagnosis is based on coexistence of the main clinical findings, such as polyneuropathy and monoclonal gammopathy associated with other clinical and laboratory features previously described.[74,76]

Treatment focuses on the underlying plasma cell disorder.[84] VEGF levels are elevated and correlate with disease activity but may not drive the process, as suggested based on the mixed results seen with anti-VEGF therapy.[76]

Diabetes mellitus

Subclinical, generalized, thicker-than-average skin changes can be found usually in patients with long-standing, severe, maturity-onset diabetes mellitus. Sclerodermalike thickened, waxy, tight skin, digital sclerosis, and limited joint mobility caused by periarticular fibrosis frequently appear both in children and adults with type 1 or type 2 diabetes mellitus without Raynaud phenomenon.[85–89] These patients usually also have mild flexion contractures of the interphalangeal joints (cheiroarthropathy or “praying hands” found in Albrecht Durer’s famous drawings on blue papers).[89–91] Scleredema may also be present in patients with diabetes who have poor metabolic control.

Hypothyroidism

Myxedema can occur in patients with severe hypothyroidism and some forms of hyperthyroidism. Hypothyroidism is most frequently seen in patients with autoimmune thyroiditis (Hashimoto disease), severe dietary iodine deficiency, or in iatrogenic causes, including postablative thyroiditis in hyperthyroid patients, neck irradiation, and certain medications.[92] Myxedema can be localized (pretibial, eye exophthalmos, involve the hands or feet, or be present in the supraclavicular fossae) or generalized.

Histologic examination of the skin shows a thickened dermis containing increased amounts of glycosaminoglycan, chondroitin sulfate, and other mucopolysaccharides in edematous spaces between collagen fibers.

The clinical findings and the changes in the total serum thyroxine and free thyroxine index tests generally confirm the diagnosis.

The primary treatment is to correct metabolic derangements as soon as possible.[23,92]

SLSs with eosinophilia

Eosinophilic fasciitis

Eosinophilic fasciitis (EF; diffuse fasciitis with eosinophilia; Shulman syndrome) is a rare disease characterized by symmetric, painful swelling, and woody induration of the skin of the extremities, in particular, over the forearms and calves (Figures 3 and 4). The middle-aged generation is mainly affected.[93] The onset is usually acute; the initial edema progresses to a coarse, orange peel (or *peau d'orange*) skin appearance (Figure 5), with hyperpigmentation and finally skin induration-tightness of a "marblelike" consistency. The trunk and the neck may also be involved. The hands and face are generally spared. Tethering of the dermis to the deeper layers causes an exaggerated deep "grooving" or "furrowing" of the subcutis over the course of the superficial veins (also called a negative vein sign) which appears on elevation of the involved extremity.[94] The superficial layers of the skin are not affected by the fibrotic process, and wrinkling of the epidermis can still be elicited by gentle pinching.

In later stages of the disease, hair loss is common in affected skin areas. Flexion contractures of the extremities and carpal tunnel syndrome may also develop. Symmetric polyarthritis of the small joints of the hands or oligomonoarthritis of the knees may also be occasionally present.[93,95] Visceral involvement is usually absent.

Spontaneous regression of the skin clinical manifestations may occur. Refractory disease or residual skin fibrosis is associated with a young (pediatric) age of onset and presence of morphea lesions and trunk involvement.[96]

As a provoking factor, heavy exertional activity may precede the onset of EF.[95] The disease may be associated with hematologic abnormalities including malignant lymphomas in 10% to 15% of the cases.[9,13] An association with other autoimmune phenomena including immune-mediated cytopenias and in particular morphea has been described.[95,97]

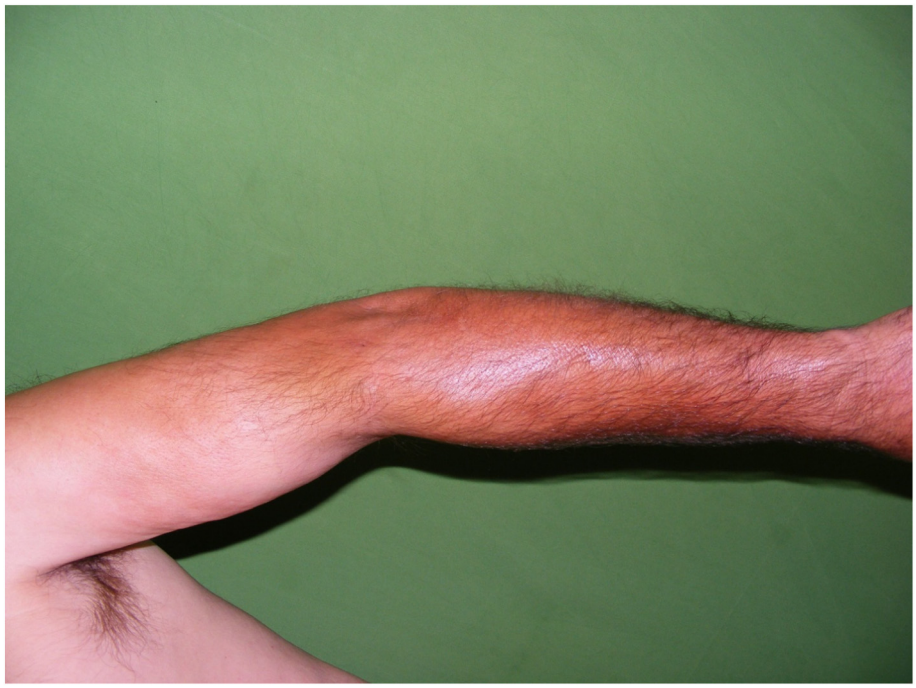

Fig. 3 Induration and erythema on the forearm in eosinophilic fasciitis.

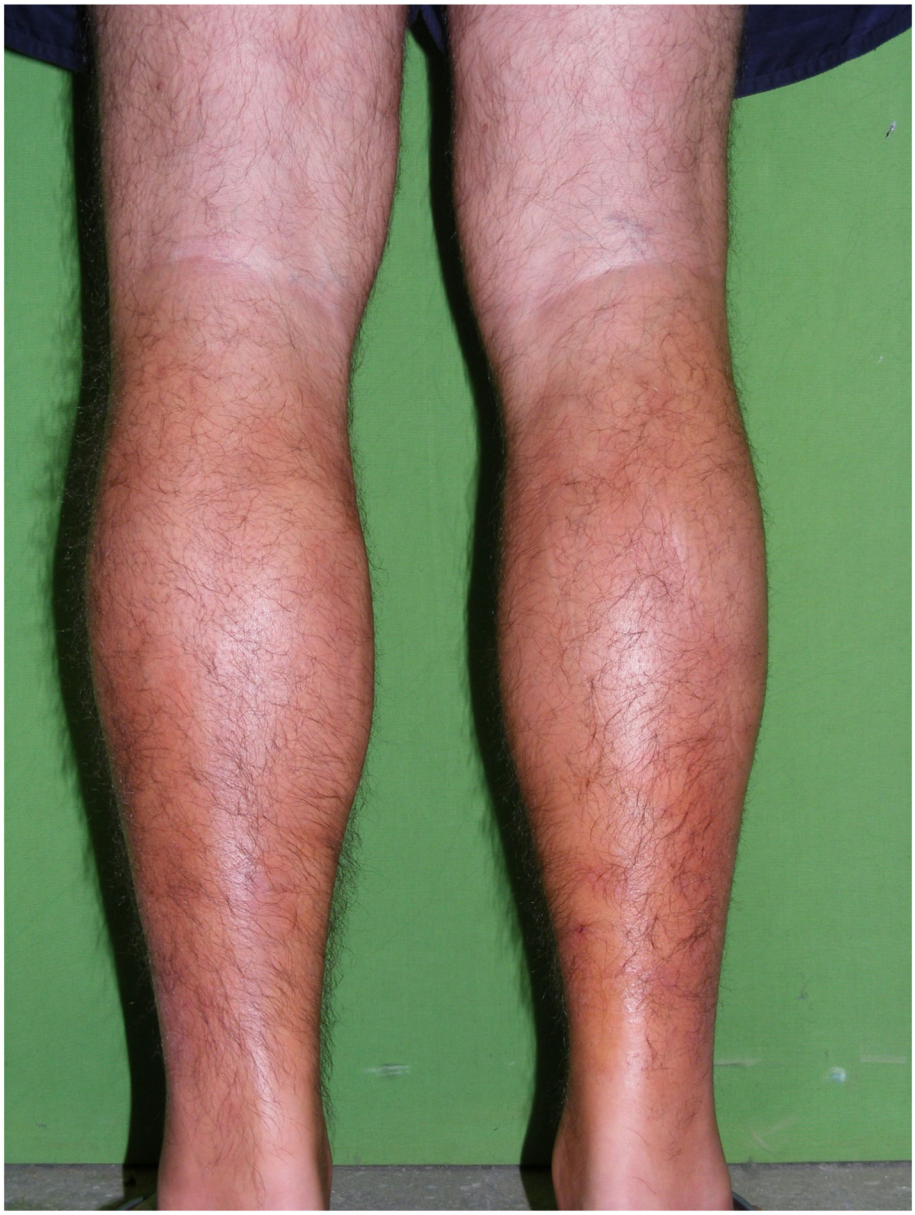

Fig. 4 Induration and erythema on the calves in eosinophilic fasciitis.

Laboratory inflammatory markers are elevated in the early phase of disease. Serum creatine kinase is normal, but serum aldolase can be elevated in active disease.[9]

The pathogenesis includes an immune response against components of the fascial and subcutaneous tissues, demonstrated by a cytotoxic inflammatory infiltrate, composed of CD8+ lymphocytes and macrophages.[98] Increased serum levels of interferon gamma, IL-10, and IL-5 secreted by mononuclear cells in the peripheral blood may play a role in the recruitment, activation, and degranulation of eosinophils.[99] Tissue fibrosis depends on the local eosinophils release of cationic granule protein, and the increase of tissue inhibitor of metalloproteinase, an inhibitor of different matrix metalloproteinases (MMPs), and decrease of MMP-13, a collagenolytic enzyme with a wide substrate specificity.[100,101]

For histologic examination, a deep skin biopsy should be performed which includes skin, fat, fascia, and superficial muscle tissue. Histology shows hyalinization and thickening affecting the deep skin layers, as well as the involvement of the fascia and the subcutis. Focal increase in eosinophils on histology and blood eosinophilia are typical signs, although they may disappear in the later stage of disease.[9,95,102] The cellular infiltrate consists of lymphocytes, plasma cells, and histiocytes. Eosinophils may be missing in the biopsies especially after administration of corticosteroid treatment. The inflammatory infiltrate predominantly consists of macrophages and CD8+ T cells with activated cytotoxic phenotype.[98] Dermal-hypodermal sclerosis, fibrotic thickening of the subcutaneous adipose lobular septa, and superficial fascia and perimysium are the hallmarks of the biopsy.

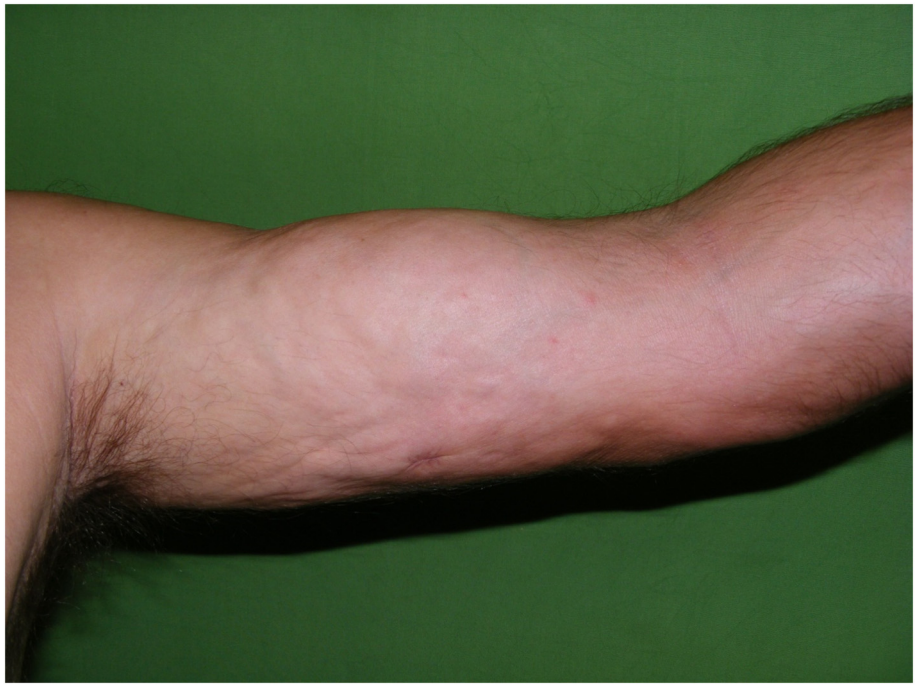

Fig. 5 Orange peel–like skin appearance in eosinophilic fasciitis.

Magnetic resonance imaging (MRI) is gaining increasing importance in the diagnosis of EF, helps in the identification of an appropriate site for tissue sampling, and provides information on treatment response.[103–105] In some case reports, ultrasound was also found useful to identify the thickening and abnormal echotexture of the skin, subcutaneous fat, tendons, and fascia of patients with EF, and these particular changes correlated with the findings on MRI.[106,107] Positron emission tomography and computerized tomography can be also useful in the diagnosis of EF as the involved fascia shows uptake of fluorodeoxyglucose corresponding to areas with clinically affected skin in some case reports.[108,109]

Two diagnostic criteria of EF have been suggested. The criteria proposed by Pinal-Fernandez and coworkers contain swelling, induration, and thickening of the skin, as well as subcutaneous tissue, fascial thickening with accumulation of lymphocytes and macrophages on biopsy as the two major criteria, and eosinophilia, hypergammaglobulinemia, muscle weakness or elevated aldolase levels, groove sign or orange peel skin, and hyperintense fascia on magnetic resonance T2-weighted images as minor criteria.[104] The diagnosis of EF is made, when both major criteria are present or if one major criterion plus two minor criteria are fulfilled.

Another diagnostic criteria proposed comprise the presence of symmetrical platelike sclerotic lesions on the four extremities as major criterion (in the absence of Raynaud phenomenon and after the exclusion of SSc), and characteristic deep skin biopsy changes (fibrosis of the subcutaneous connective tissue, with thickening of the fascia and cellular infiltration of eosinophils and monocytes) as well as thickening of the fascia on MRI, as the two minor criteria.[105] A definitive diagnosis is made when the particular case fulfills the major criterion and at least one of the two minor criteria. Validation of the proposed criteria on independent patient cohorts is still lacking.

Systemic glucocorticoids are the first-line choice therapy in EF. Prednisone is used in a dose of 0.5 to 1.0 mg/kg daily maintained until notable clinical improvement, then a slow tapering is required. Usually at least 12 to 18 months of treatment are necessary for a satisfactory response. Oral methotrexate has been used with success as glucocorticoid-sparing agent in three retrospective studies with relatively high number of patients with EF.[110–112] High doses of intravenous methotrexate (4.0 mg/kg/month) may also be considered with or without systemic glucocorticoids even in nonresponders to usual dosages of methotrexate, based on a prospective study with 12 patients.[113]

Some case reports and small clinical trials refer to the potential beneficial effect of some other immunosuppressive drugs (eg, mycophenolate mofetil, cyclosporine, azathioprine, sirolimus, dapsone, and Janus kinase inhibitors) and some biologic therapies (eg, infliximab, rituximab, tocilizumab) in patients with severe disease course in combination with the corticosteroid treatment.[111,112,114] Antithymocyte globulin and IVIG have also been reported in case reports as successful treatments for EF.[114]

Complicated cases may respond to UVA photochemotherapy with or without psoralen.[114] Physical therapy is crucial to prevent the appearance of joint contractures as 50% to 56% of patients will develop contractures during the disease course.[110,114]

SLSs linked to genetic mutations

Progeroid syndromes

Progeroid syndromes are diseases causing premature aging. Werner syndrome (WS) is a rare autosomal recessive disorder with a mutation in RecQ-type helicase.[115] Patients with WS are prone to juvenile cataract formation, metabolic disorders (eg, hypogonadism, thyroid dysfunction, diabetes, hyperuricemia, and hyperlipidemia), skin ulcers, vascular calcifications, and osteoporosis.[116,117] Sclerodermalike skin changes include atrophic skin, skin sclerosis, skin ulcers of the lower extremities, hyperpigmentation or hypopigmentation, subcutaneous calcinosis, and telangiectasia. Predominantly the extremities are affected,[7,118] A characteristic birdlike or masklike appearance and short stature with a stocky trunk and thin extremities are present. Gray hair, alopecia, and hoarseness are also the hallmarks of the disease. Early atherosclerosis and increased risk of cancer also appear. Interestingly both the collagen I to III production and MMP-1 and MMP-3 activity are increased.[116]

Other premature aging syndromes include Cockayne syndrome,[119] ataxia telangiectasia,[120] Rothmund-Thomson syndrome,[121] Hutchinson-Gilford progeria syndrome,[122,123] and insulinlike growth factor I (epidermal growth factor) deficiency, Wernerlike syndrome due to combined growth factor deficiency, and Wiedemann-Rautenstrauch syndrome.[124] Down syndrome also shows some similar characteristics.[125]

The Hutchinson-Gilford progeria syndrome belongs to the laminopathies.[123] Laminopathies are heterogeneous groups of genetic disorders due to abnormalities in type A lamins causing highly variable multisystem dystrophy syndromes.[126] Patients with laminopathies may also have sclerodermalike skin changes. Primary laminopathies are caused by the gene encoding lamin A and C. Lipodystrophy, muscular dystrophy, progeroid syndromes, mandibular dysplasia, cardiomyopathy, and restrictive dermopathy are the major clinical features. The secondary laminopathies are due to mutations in a zinc metalloproteinase gene (*ZMPSTE24*) that is involved in the processing of prelamin A.[126] Mandibuloacral dysplasia and restrictive dermopathy are the main features related to secondary laminopathies. Restrictive dermopathy is a lethal neonatal disorder caused by *LMNA* and *ZMPSTE24* gene defects.[127] The skin is shiny, sclerotic, and rigid. Micrognathism and beaked nose are present. Most probably, the fetal hypokinesia causes the tight skin and contractures.[128,129]

Acrogeria, Gottron type, is a mild, and nonprogressive skin atrophy.[130,131] Congenital abnormality in type III collagen synthesis may partly account for the pathogenesis.[132] Metageria or acrometageria is a mixture of acrogeria and clinical manifestations of WS.[133]

Melorheostosis

Melorheostosis is a rare mesodermal disorder characterized by hyperostosis of the cortex of tubular bones resembling dripping candle wax, and soft tissue abnormalities.[134,135] In some cases, the soft tissues overlying the bones may show sclerosis; the cutaneous manifestations may include sclerodermalike asymmetrical bands of sclerosis, erythema, hyperpigmentation, and fibrotic contractures.[136]

The cortical hyperostosis probably influences the proliferation of neighboring deep dermal collagen leading to the overlying sclerodermalike skin changes. The mutation of the *LEMD3* gene has been found in some cases.[137]

It is a chronic progressive disorder with no known curative treatment. Options range from nonsurgical management (eg, splinting and early training in making optimal use of the unaffected extremity) to various types of orthopedic surgical management.[138,139] Some case reports showed pain relief after bisphosphonate treatment.[140,141] One recent case report indicated the effectiveness of denosumab, a receptor activator of nuclear factor kappa-B ligand (also called RANKL) inhibitor monoclonal antibody in a patient with failure on intravenous bisphosphonate treatment.[142]

Phenylketonuria

Phenylketonuria is a rare congenital metabolic disease caused by phenylalanine hydroxylase or tetrahydrobiopterin deficiency and reduced tyrosine concentrations in the blood and tissues.[143,144] High blood level of phenylalanine has a toxic effect on the brain and is associated with several neurologic signs, for example, microcephaly, seizure, and delayed speech. The untreated phenylketonuria is also characterized by hypopigmentation (excessively fair hair and skin), and the musty smell of a baby's sweat and urine, due to phenylacetate, a carboxylic acid produced by the oxidation of phenylketone.[7,145] These particular patients often have a tendency to develop dermatitis. Sclerodermalike skin changes may be observed usually within the first 2 to 3 years of the life in the proximal parts of the extremities, sparing the hands and feet. The disease is tested for during neonatal screening, usually on the fourth or fifth day of life. Diagnosis is based on phenylalanine and decreased tyrosine concentrations in the blood (eg, Guthrie test).[146] The severity of the skin involvement usually regresses upon introduction of a strict low-phenylalanine diet. Sapropterin dihydrochloride medication may also be useful in some cases.[147]

Stiff skin syndrome

Stiff skin syndrome (SSS) is a highly heterogeneous SLS characterized by cutaneous stiffness, severe joint contractures, and progressive restriction of the chest that may lead to death.[148,149] Reported cases have had an insidious onset in infancy or in early childhood, followed by slow progressive fibrosis of areas with abundant fascia leading to immobility of the large joints, primarily or exclusively in the pelvic and shoulder girdle areas. Variable mild hypertrichosis may develop on the thighs. Usually, there are no visceral or other musculoskeletal involvements.[150,151]

There have been diverse histologic patterns described in previous reports, where the involved skin and fascia reveal thickness without inflammatory or amyloid infiltration.[150–152]

The diagnosis is supported by histopathologic findings consisting of either fascial sclerosis or an increased fibroblast cellularity with thickened, sclerotic, usually horizontally oriented collagen bundles in the deep reticular dermis or subcutaneous septa with no inflammation or distortion of adnexa and no increased spaces between the bundles. The findings of increased mucin with increased fibroblast cellularity are suggestive but not diagnostic of SSS.[151]

Early initiation of physical therapy is mandatory to prevent joint restriction and maintain quality of life. Recently used immunosuppressive therapy (eg, mycophenolate mofetil) slows the development of skin changes, but it also appears that once the skin has hardened, it cannot revert to its healthy flexible state.[148] One adult patient with SSS and multiple myeloma was successfully treated with autologous hematopoietic stem cell transplantation.[153]

The skin involvement in Parana hard-skin syndrome is similar to SSS, but it is apparently a distinct entity with severe growth failure and a more malignant course, frequently with respiratory insufficiency.[154] In another probable variant of SSS, called congenital fascial dystrophy, the collagen changes exclusively affect the enlarged fascia. This stone-hard subcutaneous induration is most involved on the thighs and buttocks, with contractures of the knees and hips.[154,155]

Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is a skin disorder caused by inherited or acquired uroporphyrinogen decarboxylase enzyme defects in the porphyrin-heme biosynthetic pathway.[156,157] PCT is characterized, compared with other porphyrias, by predominant skin manifestations and a relatively late disease onset. PCT is the most common among the porphyrias with a prevalence about 10 cases per 100,000 people in the European population. PCT type II is characterized by skin findings, affecting the areas of the skin exposed to sunlight, especially the face, ears, and the dorsal side of the hands (Figure 6). Initially, there are bullae that eventually ulcerate, along hyperpigmentation and hypertrichosis. Localized sclerodermalike changes or sclerodermalike form may develop with histologic findings almost identical to idiopathic scleroderma.[157–159]

The pathogenesis of PCT is associated with the accumulation of phototoxic porphyrins in the skin, leading to photosensitivity with erythema, hyperpigmentation, and blistering on the sun-exposed areas. The stimulatory effect of uroporphyrin on collagen biosynthesis by fibroblasts, which occurs independent of irradiation, may be responsible for the thickened lesions seen on both sun-exposed and sun-protected areas. Activated mast cell and fibroblast interaction may contribute to the development of fibrosis with a mechanism still unclear. Specific biochemical porphyrin profile for each type of porphyria helps in determining the specific diagnosis. Porphobilinogen levels in a urine sample are the initial screening test for the diagnosis of acute hepatic porphyria. Measurement of plasma and urine porphyrin levels are the initial screening tests in patients with suspected cutaneous porphyria.[156,160] Patients diagnosed with PCT obviously should avoid excess exposure to sunlight (especially in the summer), alcohol consumption, and iron supplements, as well as estrogen and chlorinated cyclic hydrocarbons, all of which can potentially exacerbate their disease. PCT is readily treatable with either repeated phlebotomy or 4-

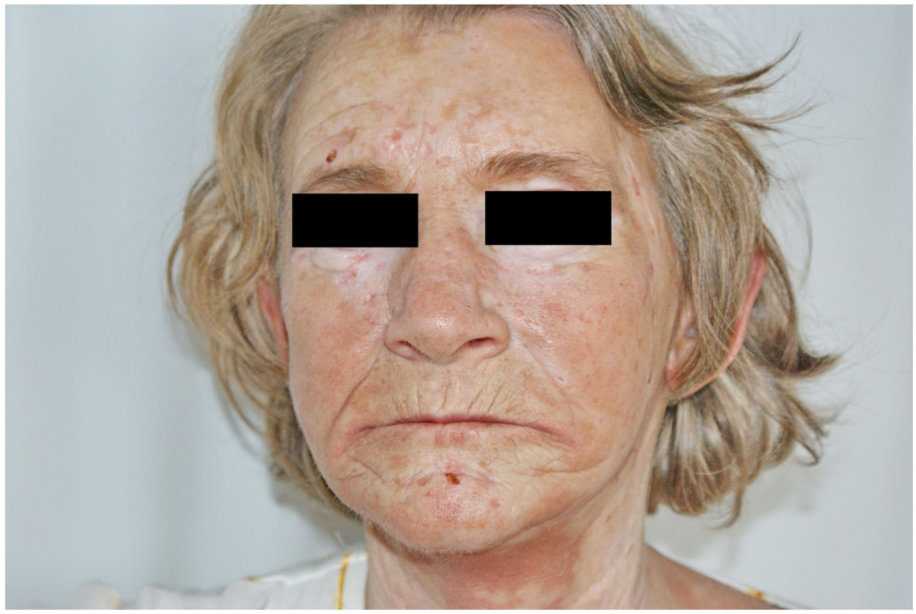

Fig. 6 Skin changes on the face in porphyria cutanea tarda.

aminoquinoline antimalarials. Relapses are somewhat more frequent after remission with 4-aminoquinoline regimens than after remission from phlebotomy.[161,162]

Drug-induced and toxic SLSs

Iatrogenic SLSs have been described after the administration of drugs including chemotherapeutic agents (eg, bleomycin, docetaxel, melphalan, tegafur/uracil, gemcitabine, paclitaxel), opioid analgesics (eg, pentazocine), amines (eg, bromocriptine), appetite suppressants, anti-Parkinson agent (eg, carbidopa), and serotonin receptor antagonist (eg, methysergide).[145,156] Intramuscular or superficial administration of vitamin K, corticosteroids, vitamin B_{12}, and pentazocin injections may also provoke localized SLS.[145,156] Some organic solvents, silica, epoxy resin, and vinyl chloride exposure may induce systemic sclerosis or localized scleroderma.[163–166]

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) appears mainly in patients with moderate-to-severe kidney failure and can affect both the skin and the internal organs (lungs, kidneys, testicles, cardiac and skeletal muscles, meninges, and the eyes).[167–172]

The use of gadolinium-based contrast agents (GBCAs) for MRI has been recognized as the specific trigger for the development of NSF.[173,174]

The early clinical signs include weakness, burning pain, pruritus, and cutaneous papules and plaques accompanied by edema; later, the skin becomes thickened, hyperpigmented, and with a peau d'orange appearance.[171,172] The disease can progress on the extremities, distally to proximally and can involve both the upper and lower extremities, sparing the face.[171,172]

The toxicity of GBCA depends on the molecular stability. The "older" linear agents were associated with the highest risk of NSF (eg, gadodiamide, gadopentetate dimeglumine, and gadoversetamide), whereas the use of the new macrocyclic and linear agents (eg, gadobenate dimeglumine and gadoxetate disodium) lead to a dramatic decrease in the incidence of NSF.[23,175] The currently available guidelines on the use of different GBCAs in patients with chronic kidney involvement also had a major effect on the prevention of new NSF cases.[176]

Diagnosis is based on the typical history and clinical findings, followed by histologic confirmation. The histology is characterized by increased dermal cellularity, thickened collagen bundles with surrounding clefts, and variable increase in dermal mucin and elastin.[23,177] The presence of CD34-positive dermal dendritic cells is also suggestive of NSF.

There are no widely accepted therapeutic options, making prevention very important.[178–180]

Other SLSs

Chronic graft-versus-host disease

Chronic graft-versus-host disease (GVHD) is the major late complication of long-time survivors of bone marrow transplantation and occurs in 40% to 80% of these patients.[181–187] Early withdrawal of immunosuppression and donor lymphocyte infusions has remarkably increased the number of patients with GVHD. Many features of chronic GVHD resemble Sjögren syndrome, primary biliary cirrhosis, and scleroderma. Skin sclerosis in chronic GVHD may be considered a form of cutaneous fibrosis with features of excessive tissue repair related to an immunologic reaction between lymphocytes of the graft and tissue host cells.

Chronic cutaneous GVHD manifestations include lichen planus–like skin changes (erythematous to violaceous papules or plaques on the dorsal surface of the hands and feet, the forearms, and the trunk, with or without fine scale) and sclerotic manifestations that include poikiloderma, lichen planus–like eruption, deep sclerotic features, morphealike superficial sclerotic features (resembling morphea or systemic sclerosis in advanced phases), or lichen sclerosus–like lesions.[188,189]

Sclerotic chronic GVHD has a progressive development. The skin involvement begins superficially and progresses into the deep layers. In the localized form, the proximal areas of the arms and legs and the trunk are affected.[190] Erythematous hypopigmented or hyperpigmented, indurated plaques of morphealike or poikilodermalike lesions appear predominantly on the lower part of the trunk. Such plaques can progress to generalized, sclerodermalike skin involvement. Due to the extensive cutaneous/subcutaneous fibrosis and contractures, there may be skin ulcerations.

In the early stage of chronic GVHD, the histopathologic features show superficial interface dermatitis, lymphocyte infiltration in a lichenoid pattern with or without satellitosis, and a vacuolar change in the basal layer, whereas dermal fibrosis with vacuolar interface changes can be seen in advanced sclerotic disease.[191]

Autoantibodies including anti–topoisomerase 1, antiexosome, anticardiolipin, or antineutrophil cytoplasmic antibodies may develop.[192]

Modification of the immunosuppressive therapy is the main treatment option. Prednisolone plus calcineurin inhibitors substantially improve the prognosis.[193] Extracorporal photopheresis has been also successfully applied in cutaneous chronic GVHD in glucocorticoid refractory cases.[194,195] Recently daclizumab, sirolimus, pentostatin, and mycophenolat mofetil[196] have also been used with some success. Rituximab has been tried by several groups with a good response rate.[196,197] Small prospective and retrospective studies have evaluated the use of imatinib[198,199] for patients with chronic GVHD and suggest some beneficial effect of imatinib in steroid resistant and sclerotic chronic GVHD.[196,197] Additional data show the remarkable efficacy of the selective Janus kinase 1/2 inhibitor

ruxolitinib in patients with chronic GVHD who are refractory to corticosteroids.[200–202]

Carcinoid syndrome associated sclerodermalike skin signs

Cutaneous scleroderma is an usually late feature of the carcinoid syndrome which is characterized by skin thickening due to dermal fibrosis. Sclerodermalike signs have been exclusively found in carcinoid syndrome cases with colorectal origin, where skin thickening appears first on the legs.[203,204]

Conclusions

SLSs are rare diseases with a very low prevalence; therefore, clinical characterization and therapeutic management are based mainly on case reports and studies with small numbers of cases. Diagnosis should rely on the combination of histopathologic examination of deep skin biopsies with the assessment of the distribution and quality of cutaneous involvement and other accompanying clinical features.

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