Sclerodermatous Graft-vs-Host Disease

Clinical and Pathological Study of 17 Patients

Pablo F. Peñas, MD; María Jones-Caballero, MD; Maximiliano Aragués, MD; Jesús Fernández-Herrera, MD; Javier Fraga, MD; Amaro García-Díez, MD

Objective: To collect and review all cases of sclerodermatous chronic graft-vs-host disease from January 1, 1982, through December 31, 2000.

Setting: University hospital in Madrid, Spain.

Patients: During the study period, 493 allogenic bone marrow transplantations were performed. Sclerotic lesions developed in 17 patients.

Results: Sclerotic lesions appeared after a mean of 529 days. Previously, 10 (59%) of 17 patients showed a leopardskin eruption. Sclerosis was generalized in 12 patients and localized in 5. Nine patients presented with rippling of the skin and 8 with lichen sclerosus lesions. We found no anti–Scl-70 or anti-centromere antibodies. Results of histological analysis showed pandermal or deep-dermal sclerosis, slight vacuolar degeneration of the basal cell layer, and follicular damage with follicular plugs. In 6 (50%) of the 12 patients with evaluable biopsy specimens, septal panniculitis was found. Squamous syringomatoplasia and mucin deposits were also detected. Treatment with high doses of prednisone and azathioprine helped in 8 of 9 patients. In 12 patients, sclerosis disappeared after 487 days.

Conclusions: Leopard-skin eruption, follicular involvement, ripply skin, and lichen sclerosus lesions have been described poorly or not at all in sclerodermatous graft-vs-host disease. The presence of lichen sclerosis, morphea, septal fibrosis, and fasciitis suggests that the sclerosis can start at and affect any level of the skin. Treatment with prednisone and azathioprine seems to halt the process. Most patients have a good prognosis with treatment. Although most lesions disappear, small areas of fibrosis may remain that do not produce any physical or functional impairment.

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C H R O N I C G R A F T-V S -H O S T
disease (cGVHD) usually appears at least 2 to 3 months after allogenic bone marrow transplantation (BMT). This complication is manifested primarily by symptoms and signs associated with the skin, gastrointestinal tract system, and liver. It is frequently, but not regularly, preceded by the acute form of GVHD and occurs in 25% to 50% of patients. The mucocutaneous manifestations of cGVHD clinically resemble a wide variety of skin diseases, including lichen planus, lichenoid eruptions, sicca syndrome, morphea, scleroderma, and lichen sclerosus. Cutaneous cGVHD can be differentiated by an early lichenoid phase and a late sclerodermatous type. Nevertheless, few data are available regarding the late sclerodermatous phase of cGVHD (ScGVHD), and no large, published series of patients describe the clinical, histological, and evolutionary aspects of ScGVHD. Most authors do not separate lichenoid and sclerodermatous cGVHD in their reports, although other authors, like us, have found that the lichenoid and sclerodermatous phases of cGVHD occur independently and may be qualitatively different immunopathologic processes.

Master et al first described ScGVHD in 1975 as sclerodermatous changes in cGVHD. Manifestations included severe skin and subcutaneous fibrosis with contractures, severe wasting, and frequent infections, with the latter often the ultimate cause of death. We have collected and reviewed all clinical and histological data of all cases of ScGVHD seen in our department.

RESULTS

BONE MARROW TRANSPLANTATION

We found 17 patients in whom clinical and histological sclerotic lesions developed, ie, 12 (71%) with genScGVHD (Table 1) and 5 (29%) with locScGVHD (Table 2).
From January 1, 1982, through December 31, 2000, 493 allogenic and 510 autologous BMTs were performed in the Hospital Universitario de la Princesa, Madrid, Spain. We reviewed clinical and laboratory variables after the appearance of Sc GVHD. All patients were included retrospectively and, although patients undergoing BMT have lifelong follow-ups in our hospital, some patients with mild disease might not have been sent to our department. We assessed age; sex; pre-BMT diagnosis; HLA typing; conditioning regimen; GVHD prophylaxis; previous occurrence of acute GVHD and/or lichenoid c GVHD; number of days after BMT; data regarding blood type; results of complete blood cell count (ie, erythrocytes, leukocytes, and platelets); levels of hepatic transaminases, alkaline phosphatase, lactate dehydrogenase, and serum immunoglobulins (ie, IgG, IgA, and IgM); protein profile; immunological profile (ie, levels of antinuclear antibodies [ANA], anti–double-stranded DNA, Ro(SSA), La(SS-B), ribonuclear protein, and Sm, Jo-1, Scl-70, anti-centromere, anti-thyroglobulin, anti-microsomal, anti-gastric parietal cell, anti-mitochondria, anti-smooth muscle, and anti-liver-kidney microsomal type 1 antibodies); and serologic data (ie, cytomegalovirus [CMV], Epstein-Barr virus, herpes simplex, herpes zoster viruses, and hepatitis B and C viruses) before and after BMT.

Eight patients were female and 9 were male, with a mean age of 29 years (range, 6–47 years). Patients 7 and 8 have been described previously. All patients underwent allogenic BMT due to chronic myelogenous leukemia (n=6), acute myelogenous leukemia (n=4), acute lymphoblastic leukemia (n=3), myelodyplastic syndrome (n=2), chronic lymphatic leukemia (n=1), and aplastic anemia (n=1). For a conditioning regimen, all patients received cyclophosphamide, associated with total body irradiation therapy in 13 patients, with busulfan therapy in 3 patients, and with antithymocytic globulin therapy in 1 patient. Donors were mismatched by sex in 6 patients (35%, including 4 with locSc GVHD and 2 with genSc GVHD); 5 of the 6 involved a female donor and a male recipient. Bone marrow transplant was obtained from HLA-identical donors with negative findings of mixed lymphocyte cultures. An ABO mismatch occurred in 8 patients (47%, including 6 with genSc GVHD and 2 with locSc GVHD), and an Rh mismatch occurred in 4 patients (24%). Two patients with genSc GVHD underwent 2 transplantations. In both cases, the second transplantation was performed using marrow from the same mismatched-sibling donor. One patient with genSc GVHD received a leukocyte infusion after the BMT and before the development of the disease. One patient with locSc GVHD needed 3 bone marrow infusions to achieve a stable graft. No statistically significant differences were found between patients with genSc GVHD and locSc GVHD.

Patients were classified as having generalized Sc GVHD (genSc GVHD) if more than 2 anatomic sites were involved, and localized (locSc GVHD) in the remaining cases. We considered Sc GVHD to have resolved when less than 2% of skin surface showed tightness and no contractures or functional limitations could be found.

All histological material was collected and reviewed. Data regarding the following items were specifically evaluated and recorded: (1) vascular degeneration of the basal cell layer of the epidermis; (2) presence of necrotic keratinocytes, type and density of inflammatory cells, presence of melanophages, involvement of eccrine glands and pilosebaceous units, endothelial cell changes, and subcutaneous tissue alterations. The criterion for the presence of fibrosis consisted of thickened, homogenized collagen bundles somewhere in the dermis with narrow or absent spaces between them.

Lichenoid c GVHD was diagnosed when clinical and histological evidence was found. As most patients undergoing a BMT present with slight vascular degeneration of the basal cell layer of the epidermis, lichenoid dermatitis was histologically diagnosed when the following criteria were met: vascular degeneration of the basal cell layer, significant inflammatory infiltrate in the papillary dermis, hypergranulosis, and hyperkeratosis. Biopsy specimens showing only slight vascular degeneration of the basal cell layer with no inflammatory infiltrate or other epidermal changes were classified as vascular-type interface dermatitis.

We analyzed data using Statview 5.1 for Macintosh (SAS Institute Inc, Cary, NC), with x², Mann-Whitney, or Wilcoxon signed rank tests where appropriate.

<table>
<thead>
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<th>PATIENTS AND METHODS</th>
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<td>From January 1, 1982, through December 31, 2000, 493 allogenic and 510 autologous BMTs were performed in the Hospital Universitario de la Princesa, Madrid, Spain. We reviewed clinical and laboratory variables after the appearance of Sc GVHD. All patients were included retrospectively and, although patients undergoing BMT have lifelong follow-ups in our hospital, some patients with mild disease might not have been sent to our department. We assessed age; sex; pre-BMT diagnosis; HLA typing; conditioning regimen; GVHD prophylaxis; previous occurrence of acute GVHD and/or lichenoid c GVHD; number of days after BMT; data regarding blood type; results of complete blood cell count (ie, erythrocytes, leukocytes, and platelets); levels of hepatic transaminases, alkaline phosphatase, lactate dehydrogenase, and serum immunoglobulins (ie, IgG, IgA, and IgM); protein profile; immunological profile (ie, levels of antinuclear antibodies [ANA], anti–double-stranded DNA, Ro(SSA), La(SS-B), ribonuclear protein, and Sm, Jo-1, Scl-70, anti-centromere, anti-thyroglobulin, anti-microsomal, anti-gastric parietal cell, anti-mitochondria, anti-smooth muscle, and anti-liver-kidney microsomal type 1 antibodies); and serologic data (ie, cytomegalovirus [CMV], Epstein-Barr virus, herpes simplex, herpes zoster viruses, and hepatitis B and C viruses) before and after BMT. Eight patients were female and 9 were male, with a mean age of 29 years (range, 6–47 years). Patients 7 and 8 have been described previously. All patients underwent allogenic BMT due to chronic myelogenous leukemia (n=6), acute myelogenous leukemia (n=4), acute lymphoblastic leukemia (n=3), myelodyplastic syndrome (n=2), chronic lymphatic leukemia (n=1), and aplastic anemia (n=1). For a conditioning regimen, all patients received cyclophosphamide, associated with total body irradiation therapy in 13 patients, with busulfan therapy in 3 patients, and with antithymocytic globulin therapy in 1 patient. Donors were mismatched by sex in 6 patients (35%, including 4 with locSc GVHD and 2 with genSc GVHD); 5 of the 6 involved a female donor and a male recipient. Bone marrow transplant was obtained from HLA-identical donors with negative findings of mixed lymphocyte cultures. An ABO mismatch occurred in 8 patients (47%, including 6 with genSc GVHD and 2 with locSc GVHD), and an Rh mismatch occurred in 4 patients (24%). Two patients with genSc GVHD underwent 2 transplantations. In both cases, the second transplantation was performed using marrow from the same matched-sibling donor. One patient with genSc GVHD received a leukocyte infusion after the BMT and before the development of the disease. One patient with locSc GVHD needed 3 bone marrow infusions to achieve a stable graft. No statistically significant differences were found between patients with genSc GVHD and locSc GVHD. Patients were classified as having generalized Sc GVHD (genSc GVHD) if more than 2 anatomic sites were involved, and localized (locSc GVHD) in the remaining cases. We considered Sc GVHD to have resolved when less than 2% of skin surface showed tightness and no contractures or functional limitations could be found. All histological material was collected and reviewed. Data regarding the following items were specifically evaluated and recorded: vascular degeneration of the basal cell layer of the epidermis, presence of necrotic keratinocytes, type and density of inflammatory cells, presence of melanophages, involvement of eccrine glands and pilosebaceous units, endothelial cell changes, and subcutaneous tissue alterations. The criterion for the presence of fibrosis consisted of thickened, homogenized collagen bundles somewhere in the dermis with narrow or absent spaces between them. Lichenoid c GVHD was diagnosed when clinical and histological evidence was found. As most patients undergoing a BMT present with slight vascular degeneration of the basal cell layer of the epidermis, lichenoid dermatitis was histologically diagnosed when the following criteria were met: vascular degeneration of the basal cell layer, significant inflammatory infiltrate in the papillary dermis, hypergranulosis, and hyperkeratosis. Biopsy specimens showing only slight vascular degeneration of the basal cell layer with no inflammatory infiltrate or other epidermal changes were classified as vascular-type interface dermatitis. We analyzed data using Statview 5.1 for Macintosh (SAS Institute Inc, Cary, NC), with x², Mann-Whitney, or Wilcoxon signed rank tests where appropriate.</td>
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</table>
Clinical sclerotic lesions appeared at a mean of 529 days (range, 193–1001 days) after BMT. Previously, 10 patients (59%) showed an eruption of multiple, hypopigmented macules covered with fine scales that resembled leopard skin (Figure 1). In 4 patients, the macules evolved to a lichenoid eruption (Table 3). Follicular keratosis and follicular plugs were dispersed in the trunk and limbs in 7 patients (41%).

Sclerodermatous cGVHD was generalized in 12 patients (Figure 2), with disseminated, hyperpigmented, sclerodermatous lesions; occasional follicular plugs on the trunk and extremities; and diffuse induration or morphea-like plaques. Sclerotic lesions appeared in the trunk and became generalized in a few weeks, spreading to the extremities. In 1 patient, some of the sclerotic lesions appeared in areas of previous injury such as injections, and in another they started over a herpes zoster scar. In 9 (75%) of the 12 patients, the skin became irregularly thickened, with depressed areas lineally disposed on the extremities, giving a ripply appearance (Figure 3). Joint retractions developed, mainly on the hands, in 7 (58%) of the 12 patients. Although all 7 required rehabilitation, lesions resolved in all but patient 3. Other associated lesions were poikilodermatosis (n=3), pyogenic granuloma-like lesions (n=2), blisters and ulcers (n=2), adipose tissue eventrations (n=2), anetoderma (n=1), and nail dystrophy (n=1).

Five patients presented with locScGVHD, limited to the trunk in 3 patients (on varicella lesions in 1 of these), to the thighs in 1 patient (where he had had coxitis due to salmonellosis), and on the left leg in 1 patient (on the residual lesions of herpes zoster).

Five patients with genScGVHD and 3 with locScGVHD presented with glistening, pearly white plaques with follicular plugs similar to those of lichen sclerousus (Figure 4) that were confirmed by histological examination in 3 patients (Figure 5). The plaques were seen intermixed with morphea-like lesions. In only 3 (38%) of the 8 patients, lichen sclerousus-like lesions were the initial presentation of ScGVHD.

EXTRACUTANEOUS INVOLVEMENT

None of the patients had Raynaud phenomenon. All patients with genScGVHD showed cGVHD involvement of organs other than the skin. Although 9 patients complained of xerophthalmia, results of the Schirmer test and/or fluorescein staining were pathologic in 5. Six of these 9 patients also complained of xerostomia. Liver (n=8), lungs (pulmonary hypertension [n=2] and obstructive lung disease [n=3]), joints (n=4), and the gastrointestinal tract (n=3) were also involved.

Three patients with locScGVHD showed evidence of lung disease (mild restrictive [n=2] and obstructive [n=1]), with hepatic cGVHD in 2 of these. Another patient had liver involvement with veno-occlusive dis-
ease. Four patients complained of xerophthalmia, but only 1 patient presented with a pathologic result of the Schirmer test, and only 1 patient complained of xerostomia.

LABORATORY DATA

Red and white blood cell counts were within reference ranges for all patients, and only 1 patient showed thrombocytopenia. Ten patients with genScGVHD (83%) and 2 with locScGVHD (40%) showed elevated transaminase levels (aspartate aminotransferase, glutamic pyruvic transaminase, and/or L-glutamyltransferase); 9 with genScGVHD (75%) and 2 with locScGVHD (40%) showed elevated lactic dehydrogenase levels. All patients showed elevated phosphatase alkaline levels. Cholesterol levels of higher than 250 mg/dL (6.5 mmol/L) were found in 4 patients with genScGVHD (33%).

Six patients with genScGVHD (50%) and 3 with locScGVHD (60%) showed elevated transaminase levels (aspartate aminotransferase, glutamic pyruvic transaminase, and/or γ-glutamyltransferase); 9 with genScGVHD (75%) and 2 with locScGVHD (40%) showed elevated lactic dehydrogenase levels. All patients showed elevated phosphatase alkaline levels. Cholesterol levels of higher than 250 mg/dL (6.5 mmol/L) were found in 4 patients with genScGVHD (33%).

Although serologic studies were performed for Epstein-Barr virus, CMV, herpes simplex, herpes zoster virus, and hepatitis B and C viruses, no differences between pre- and post-BMT results were found except for CMV. Findings for CMV showed a statistically significant titer elevation. Ten patients with genScGVHD (83%) and 2 with locScGVHD (40%) had had a CMV infection by the time of the sclerosis (mean time, 308 days before). Although 12 patients presented with positive serologic findings for CMV before BMT, and 12 donors had positive findings, only in 8 cases were results positive for both. Two patients with genScGVHD showed positive post-BMT serologic findings for hepatitis C virus, and 1 of these had positive findings for hepatitis B surface antigen.

HISTOPATHOLOGY

We obtained 85 biopsy specimens from our patients, 35 of them related to the ScGVHD phase (Table 3). Specimens were obtained from the first, hyperpigmented phase of disease in 4 patients with genScGVHD (33%).

Although serologic studies were performed for Epstein-Barr virus, CMV, herpes simplex, herpes zoster virus, and hepatitis B and C viruses, no differences between pre- and post-BMT results were found except for CMV. Findings for CMV showed a statistically significant titer elevation. Ten patients with genScGVHD (83%) and 2 with locScGVHD (40%) had had a CMV infection by the time of the sclerosis (mean time, 308 days before). Although 12 patients presented with positive serologic findings for CMV before BMT, and 12 donors had positive findings, only in 8 cases were results positive for both. Two patients with genScGVHD showed positive post-BMT serologic findings for hepatitis C virus, and 1 of these had positive findings for hepatitis B surface antigen.

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ScGVHD in patients with no previous acute or lichenoid cutaneous GVHD. Moreover, of the 7 patients with previous lichenoid cGVHD, 5 showed vacuolar degeneration in the results of biopsy of the sclerosis, whereas 9 of the 10 patients with no previous lichenoid cGVHD did. Vacuolar degeneration was even more intense in the follicular epithelium in 10 cases. This follicular damage was accompanied in 8 patients by conspicuous follicular plugs, with milia cysts in 3 of them (Figure 6). Moreover, of the 11 biopsy specimens with follicular plugs, 10 showed conspicuous vacuolar degeneration, whereas none of the 12 without vacuolar degeneration showed follicular plugs. Hyperpigmentation was a constant clinical feature of our patients, as reflected by the presence of melanophages in all patients and hyperplastic melanocytes in 15 (88%) of them. In the 7 biopsy specimens obtained 360 days after ScGVHD diagnosis, slight vacuolar degeneration was found in 3 and follicular plugs in 2, although all showed fibrosis.

Fibrosis was one of our inclusion criteria for the study (Figure 7). Pure superficial sclerosis was found in 4 biopsy specimens from 3 patients, but most of them showed pandermal or deep-dermis sclerosis (Table 4). Of the 12 specimens obtained in the first 60...
days of evolution, 2 (17%) showed superficial sclerosis; 3 (25%), patched sclerosis; 3 (25%), pandermal sclerosis; and 4 (33%), deep-dermis sclerosis. In patient 7, the fascia was affected by the sclerotic process. Lichen sclerosus–like lesions showed epidermal atrophy, hyperkeratosis with follicular plugs, and edema and homogenization of the collagen in the upper dermis (Figure 5). Inflammatory infiltrate was patchy, with a bandlike appearance. We found septal panniculitis (Figure 8) in 6 (50%) of the 12 patients with evaluable specimens (all with genScGVHD), showing deep dermal sclerosis, and all of these patients presented clinically with rippling of the skin. In 2 patients, septal panniculitis appeared in biopsy specimens obtained during the first 60 days of evolution. An additional patient showed fibrosis in the hypodermis. Pilosebaceous units in 9 patients and eccrine glands in 7 were clearly diminished or even disappeared. Squamous syringometaplasia was found in 2 patients with genScGVHD; mucin deposits, dispersed in the dermis, were found in 5 patients with genScGVHD.
No conspicuous evidence of endothelial damage was found.

**TREATMENT AND EVOLUTION**

Nine patients were treated with high dosages of prednisone (1 mg/kg) and azathioprine (approximately 1.5 mg/kg) during the active phase of ScGVHD (1-6 months), with slow tapering during the stabilization and resolution of the disease (7 months to 2 years). Two patients received prednisone and cyclosporine, and the last patient received cyclosporine alone. In 1 patient, locScGVHD resolved only with topical clobetasol propionate.

Two of the patients received treatment with thalidomide. After 3 years and 4 months without improvement while receiving azathioprine and prednisone or cyclosporine, patient 3 was treated with thalidomide (300-800 mg/d) when her ScGVHD was no longer active. Very slow progressive improvement was observed during the 2 years of treatment and, although the drug therapy was stopped 9 years ago, she is still slowly improving. Patient 6 was initially treated with thalidomide (200 mg every 6 hours) during 6 months at the beginning of the disease without effect. The drug therapy was discontinued, and standard treatment with azathioprine and prednisone was started. After 6 months, the disease began to resolve, and doses of prednisone were slowly tapered.

The ScGVHD disappeared after a mean of 487 days (range, 215-1180 days) in 12 patients. Mean time to resolution in patients with locScGVHD was significantly shorter (246 vs 607 days; *P* = .02). The disease remains in patient 3 after 3104 days; patient 13 died owing to an unrelated cause just after the diagnosis of ScGVHD; and the last 3 patients have received recent diagnoses.

We have followed up our patients for a mean of 7.6 years (range, 1-16.3 years), with a mean time since the finish of their treatment of 6.6 years (range, 0-13.6 years). Late in the evolution of the disease, residual hyperpigmentation and small areas with histological evidence of fibrosis remained, although sometimes no induration was detected by palpation. This residual sclerosis does not interfere with their activities or require any special care.

![Figure 7. Thickened, homogenized collagen bundles extending over the whole dermis.](https://jamanetwork.com/)

### Table 4. Histological Findings

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*EVD indicates epidermal vacuolar degeneration; FVD, follicular vacuolar degeneration; FP, follicular plugs; fibrosis, localization of fibrosis in the biopsy specimens; Sup, superficial; Med, media; Pand, pandermal; Patch, patched; pannic, panniculitis; Si, slight; LEA, lichen sclerosus; NE, not evaluable; and ellipses, not applicable.*
published, but most of them are related to treatment results, with few data regarding clinical or histological findings or dermatological evolution. Worst of all, data from the different dermatological forms of cGVHD are frequently mixed in the same report. We have herein reviewed 17 cases of ScGVHD diagnosed in our department.

Since the first cases, all authors, to our knowledge, have reported the resemblance of ScGVHD to systemic sclerosis. Although Raynaud phenomenon develops in virtually all patients with a diagnosis of systemic sclerosis,20 none of our patients with ScGVHD showed this phenomenon. Clinically, none of our patients underwent an edematous phase of systemic sclerosis. Moreover, no Scl-70 or anti-centromere antibodies were detected, and no female predominance was found. In most previously described patients, these items (Raynaud phenomenon, edematous phase, and autoantibodies) are rarely reported as positive findings.2,16-18 All of these data suggest that, although most patients fulfill the criteria of the American College of Rheumatology for systemic sclerosis,21 both diseases could have different etiopathogeneses.

Bone marrow transplantation involves chimerism, and some authors suggested that this could be the etiologic factor. The homogeneous genetic background of the Japanese population has been claimed as the cause of the low frequency of cGVHD observed in that population.20 Following this rationale, the cellular microchimerism theory has been shown as a possible explanation of the pathogenesis of systemic sclerosis,21 although some doubts have been raised recently.22

Shulman et al5,23 classified disease in their patients as generalized and localized. Patients with generalized disease followed a biphasic course, with first a generalized erythematous or violaceous rash, and then poikiloderma with sclerotic hidebound skin. Dermal induration with no previous lichenoid phase developed in those with localized disease. Patients were diagnosed as having a lichenoid eruption even if they had only histological findings. Chosidow et al2 also found that lichenoid cGVHD always preceded the sclerodermatous phase. Using our criteria, only 4 (33%) of our patients with genScGVHD had a previous lichenoid eruption, and 3 (60%) of our 5 patients with locScGVHD had lichenoid lesions in the sclerotic area. We therefore classified ScGVHD as generalized and localized disease, with no reference to a previous lichenoid phase. This classification agrees with those of other authors who have found that lichenoid and sclerodermatous cGVHD occur independently.7,8

Nevertheless, most of the biopsy results of our patients with ScGVHD showed vacuolar degeneration in the basal cell layer of the epidermis and some necrotic keratinocytes, suggestive of interface dermatitis but not enough to classify them histologically as lichenoid. Several authors2-5 reported vacuolar degeneration as a rare finding in ScGVHD, and that when found, it may indicate an earlier lesion that is still evolving.7,16 We found vacuolar degeneration in the epidermis of 9 (90%) of 10 patients with no previous lichenoid cGVHD, even in biopsy specimens obtained 1 to 4 years after the diagnosis of ScGVHD, and in 5 (71%) of 7 patients with previous lichenoid cGVHD. This suggests that factors other than the presence or intensity of the lichenoid reaction should be used to explain the presence of vacuolar degeneration of the basal cell layer of the epidermis.

We want to emphasize the leopard-skin eruption (widespread, well-delimited, hyperpigmented macules) that appeared in 6 (50%) of the 12 patients with genScGVHD before the sclerotic changes. Shulman et al5 reported that in 10 (63%) of their patients with generalized involvement, eruption evolved from diffuse, nonuniform hyperpigmentation with a cobblestone pattern, to poikiloderma and induration with no clinical lesions, resembling lichen planus. Other authors have stated that these pigmented changes precede, almost constantly, the development of evident sclerosis and are very distinctive.16 Histologically, we found sclerosis in the reticular dermis and, in most of these patients, slight vacuolar degeneration of the epidermis, with no other findings suggestive of a lichenoid eruption.

Follicular involvement has been previously described only in patients with lichenoid cGVHD.24,25 We saw follicular keratosis in the first phases of the ScGVHD and observed that it disappears during the evolution of the disease and that it does not follow the pattern of the leopard-skin eruption. Histologically, follicular keratosis has a good correlation with the presence of vacuolar degeneration in the epidermis and follicular walls. This follicular damage is probably the cause of the follicular plugs and epidermal cysts we have seen. Although it suggests that the follicle could be the starting point of the sclerotic process in our patients, and although 1 of the biopsy results showed...
folicular-centered fibrosis, we cannot rule out the possibility that it merely indicates a second target in the ScGVHD process.

Squamous syringometaplasia has been described rarely in cGVHD, always in relation to lichenoid cGVHD. We have found squamous syringometaplasia in typical ScGVHD.

Lichen sclerosus–like lesions have been described rarely. Only Chosidow et al reported that 29% of their patients presented with atrophic, pearly white plaques. We have found lichen sclerosus–like lesions in 8 (47%) of our patients and, in the 3 of these patients undergoing biopsy, histological findings of lichen sclerosus were found. Although some authors suggest that lichen sclerosus represents a superficial type of morphea, and although we cannot exclude it, our clinical and histological findings are within the range of classic lichen sclerosus. Remarkably, in 5 of our 8 patients, these lesions appeared late in the evolution of ScGVHD.

From our point of view, the 3 main histological sclerotic patterns are pandermal, patched, and deep dermal. Others have suggested that the sclerotic process starts and predominates in the upper dermis, and some ultrastructural findings support this hypothesis. Nevertheless, Chosidow et al did not find any upper dermis predominance, and we have not seen it in our patients. In fact, only 2 of the 12 biopsy specimens obtained in the first 60 days showed pure superficial sclerosis.

Another overlooked clinical finding was the presence of rippling of the skin that we found in 75% of our patients with genScGVHD. Only Shulman et al reported that cGVHD occasionally produces a rippled fibrotic appearance similar to eosinophilic fasciitis. The absence of ripply skin on locScGVHD suggests that this sign could be a marker of the severity of the process, and that it is related to the presence of septal panniculitis only in patients with genScGVHD. In this regard, septal panniculitis has not been previously described as a histological type of ScGVHD. Although Shulman et al reported lobular panniculitis in the early lichenoid phase of cGVHD, other authors use the presence of dermothypodermal or even hypodermal involvement to suggest systemic sclerosis or morphea that is absent in ScGVHD. Janin et al have found septal infiltration and fibrosis in patients with cGVHD and clinical and histological diagnoses of fasciitis. Only 1 of our patients with septal panniculitis showed clinical symptoms and signs suggestive of fasciitis; therefore, biopsy including fascia was not performed in the others. Because the patients of Janin et al did not show any dermal involvement, the authors concluded that the fasciitis in cGVHD was a distinct entity with further subcutaneous tissue involvement; whereas our patient with clinical fasciitis showed deep dermal sclerosis, septal panniculitis, and fasciitis. Moreover, all of our patients with septal panniculitis showed reticular dermis sclerosis. Clinically, all patients with hypodermal involvement presented with ripply skin, suggesting that this histological finding can be missed if the biopsies are not made deep enough. Chosidow et al reported that 4 of their 7 patients showed fibrosis in the dermis extending to the subcutaneous fat, and this evolution has been suggested in 2 recent reviews.

The presence in our patients of lichen sclerosus–like lesions, morphea-like lesions, and ripply skin and the histological findings of septal fibrosis and fasciitis suggest that the sclerosis in ScGVHD can start and affect any level of the skin and can extend to involve the complete dermis, the subcutis, and even the fascia.

Poikiloderma was described as a frequent finding in the first reports of cGVHD. Since then, it has been infrequently described, although results of ultrastructural studies showed dilated dermal capillaries. Vascular tumors have been described in patients with ScGVHD, but anetoderma has not been reported as a late complication of ScGVHD.

Mucin deposits within vacuolated spaces have been found in 3 patients with ScGVHD. We have found mucin deposits in 5 of our patients, with no presence of vacuolated spaces. Mucin may be trapped within grossly sclerotic connective tissue, but an excess of production by activated fibroblast cannot be excluded.

Most authors who described patients with cGVHD combine lichenoid and sclerodermatous cGVHD. In an early report, Shulman et al described the presence of contractures, chronic ulceration, muscular wasting, kyphoscoliosis, keratoconjunctivitis sicca, stomatitis, and painful burning of the feet as the main complications of ScGVHD. In 7 patients, Chosidow et al found 6 with reduced lacrimal secretion and 5 with pulmonary abnormalities, with no reference to liver involvement except for 2 patients with cirrhosis. We also found a high presence of lacrimal involvement and clinical salivary abnormalities. Pulmonary diseases were also frequent in our patients, but 12 (71%) of our 17 patients presented with elevated hepatic transaminase levels at the time of the diagnosis of ScGVHD.

Previous studies have implicated pre-BMT positive serologic findings for CMV in donors and/or recipients as a risk factor for cGVHD, especially if both had positive findings. In our study, we have found a statistically significant change in the pre- vs the post-BMT serologic titers for CMV, with no changes in findings for Epstein-Barr virus, herpes simplex, or herpes zoster virus. In 47% of the patients, pre-BMT serologic findings for donors and recipients were positive.

Studies of autoantibodies in ScGVHD reflect wide discrepancies between different groups. Bell et al found anti–Scl-70 antibodies in 21% of their patients with ScGVHD, whereas other studies, including ours, did not find anti–Scl70 antibodies. Bell et al also found ANA in 95% of their patients, but we have found it in 50% of our patients with genScGVHD, and Chosidow et al in 29%. Chosidow et al reported a high prevalence of anti–smooth muscle antibodies (71%), whereas we have found them only in 2 patients.

Bell et al found a high prevalence of HLA-A1 (63%) and HLA-B1/B2 (42%). We have found only 3 patients with HLA-A1 (20%) and none with HLA-B1/B2. This finding may be explained by the genetic differences of our populations. In this regard, the low frequency of cGVHD in Japanese patients compared with those from the United States or Europe has led Fujii et al to suggest that the
difference may be related to the genetic background of the Japanese.

Extensive cGVHD should be treated. Untreated patients in whom contractures developed did not show subsequent evidence of spontaneous improvement of skin disease and became crippled. Sullivan et al reported that 76% of the patients treated with immunosuppressive combination therapy were free of disease, compared with 23% of inadequately treated and 18% of untreated patients.

Different agents that have been tried include prednisone, cyclophosphamide, procarbazine hydrochloride, azathioprine, antithymocytic globulin, electron-beam radiation therapy, penicillamine, cyclosporine, psoralen-U-VA therapy, thalidomide, clofazimine, extracorporeal photochemotherapy, etretinate, or various combinations. Treatment of cGVHD with prednisone alone seemed to be less effective than combination therapy, so different combinations were tried. Although prednisone and azathioprine were effective, a study showed that this combination conveys a high risk for death due to infectious diseases, and the association of cyclosporine and prednisone was suggested as a better option. Responses to thalidomide treatment have been seen in patients with lichenoid, sclerodermatous, oral, ocular, and hepatic involvement with GVHD. In our study, thalidomide did not show any clear benefit in cutaneous lesions. A recent report has shown that thalidomide could be effective in the treatment of cGVHD that did not include severe sclerodermatous manifestations. This limitation has also been described for psoralen-U-VA therapy. Clofazimine has been used to treat 6 patients with ScGVHD with 3 partial responses, 2 patients with stable disease, and 1 patient with no response. Extracorporeal photochemotherapy was used in 12 patients with ScGVHD gave 75% complete responses and 25% partial responses. A recent study reported a very good response of ScGVHD to etretinate after disease has not responded to other treatments. Of 27 patients with evaluable disease, the authors obtained improvement in 74%, among whom 2 patients have had a complete response. We have treated ScGVHD in 9 patients with high doses of steroids and azathioprine and obtained complete responses in 3 and no response in 1 of these patients (patient 3). This regimen has been shown to significantly worsen outcomes in a randomized study of cGVHD, as the authors observed a doubled rate of mortality (21%-40%), mostly due to infections. These differences could be explained by different cohorts (cGVHD vs ScGVHD), the small number of patients in our series, or improvement of supportive treatment in cGVHD. In our hands, this treatment seems effective to halt the progression and even to resolve the skin process without severe adverse effects or complications, but this treatment may not represent optimal treatment for patients with GVHD outside this cohort.

We have found few data regarding the resolution of symptoms. In our series, we found that most patients have a good prognosis after immunosuppressive treatment. Of the 12 patients receiving this therapy, 11 (92%) are free of disease, and lesions remain in 1 patient. Although most lesions disappear in the course of the disease, small areas of fibrosis remain that usually do not produce any physical or functional impairment.

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