LETTER TO THE EDITOR

CLINICAL, SEROLOGIC AND INSTRUMENTAL DATA OF TEN PATIENTS AFFECTED BY SCLERODERMATOUS CHRONIC GRAFT VERSUS HOST DISEASE: SIMILARITIES AND DIFFERENCES IN RESPECT TO SYSTEMIC SCLEROSIS

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Chronic graft versus host disease (cGVHD), the most common late complication of allogeneic haematopoietic stem cell transplantation (HSCT), may present with sclerodermatous lesions resembling in some cases the cutaneous involvement of systemic sclerosis (SSc). Certain pathogenetic findings connect the two diseases. In this report we describe ten subjects affected by cGVHD who underwent the examinations routinely carried out to stage SSc patients. Demographic, clinical, serologic and instrumental data were recorded. These patients showed differences in appearance, extent and progression of the sclerodermatous lesions with greater involvement of the trunk and proximal part of the limbs than the extremities. In seven subjects ANA test was positive; scleroderma-associated autoantibodies were not detected in any of the cases. Moreover, typical organ involvement of SSc was not found. Only one patient developed Raynaud's phenomenon after HSCT and only one patient demonstrated a nailfold videocapillaroscopic scleroderma pattern. Except for cutaneous involvement of cGVHD, that may resemble SSc, the clinical features of the two diseases are quite different, suggesting that the fibrotic process characterizing cGVHD and SSc has different etiologies and different initial pathobiologic events.

Chronic graft-versus-host disease (cGVHD) is the most serious long-term complication of allogeneic Haematopoietic Stem Cell Transplantation (HSCT), occurring in 30% to 70% of patients surviving more than 100 days. cGVHD may present with a wide variety of cutaneous manifestations which are classically divided into three major clinical categories, as reported in Table I (1-2). The skin lesions may resemble cutaneous manifestations of SSc; the similarity of skin involvement between the two diseases led Nelson et al. to raise an etiopathogenetic hypothesis concerning SSc which implicates microchimerism (3).

Some animal models of cGVHD have been developed with the aim of clarifying the complex phenomena that cause cutaneous and visceral fibrosis. Both donor CD4+T and B cells in transplants are required to induce cGVHD (4). In the early phase of the disease donor monocyte/macrophage and T cells infiltrate the skin; another precocious event is represented by TGF-β1 production together with chemokines release, that precedes the development of fibrosis (5). The process may be suppressed by donor Treg cells (4) and by antibodies against TGF-

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β1 (5).

Regarding autoantibodies, it was reported that of 19 patients with scleroderma-like cGVHD 18 cases showed positivity for ANA at title of 1:640 or higher and 11 for antinucleolar antibodies; moreover antibodies against Scl70, PM-Scl and SS-B antigens were detected in 4, 2 and 1 cases, respectively (6). Our work aims to subject patients affected by sclerodermatous cGVHD to the same investigations which are routinely performed to assess SSc patients in order to find clinical similarities and differences.

MATERIALS AND METHODS

Between October 2005 and August 2008, we enrolled 10 consecutive patients affected by scleroderma-like cGVHD treated at the Department of Hematology of the University Hospital in Verona. Four patients were female and six were male, with a median age of 40 years (range: 29-61 years); the length of follow-up from the cGVHD onset was 51 ± 26 months. All patients underwent allogeneic HSCT due to acute myelogenous leukemia (6 cases), acute lymphoblastic leukemia (1 case), myelodysplastic syndrome (2 cases) and T-cell anaplastic non-Hodgkin lymphoma (1 case). HSCT was obtained from HLA-identical donors. For a conditioning regimen, all patients received cyclophosphamide, associated with total body irradiation therapy. For GVHD prophylaxis, the patients were given methotrexate and cyclosporine.

The diagnosis and grading of cGVHD were primarily based on clinical findings and were in agreement with the commonly accepted diagnostic criteria (7). The following were evaluated: the interval time between HSCT and the onset of cGVHD; complete blood cell count; liver and renal function indices; autoimmune profile comprehensive of ANA detected by indirect immunofluorescence test on HEp-2 cell substrate at the initial dilution of 1:80, anti-ENA antibodies by ELISA method and anti–smooth muscle antibodies by indirect immunofluorescence test; serologic data concerning Cytomegalovirus (CMV), Epstein-Barr virus, Parvovirus B19 before and after HSCT.

The visceral involvement was evaluated in all the patients by chest radiograph, electrocardiogram, colourDoppler echocardiogram, and pulmonary function test with diffusing capacity for carbon monoxide adjusted to hemoglobin; esophageal manometry was performed in 5 cases. Nailfold videocapillaroscopy (NVC) was carried out and the microvascular alterations were classified into 3 different patterns: "early", "active" and "late".

RESULTS

The demographic, clinical and serologic findings of the patients are summarized in Table II. Sclerodermatous lesions appeared after a mean of 27.2±23.0 months from HSCT. Sclerodermatous cGVHD was generalized in four patients (pts 1-4) with disseminated sclerotic lesions, resembling those of "pansclerotic" morphea; except in one subject (pt 4) in which they appeared on the trunk and widespread quickly to extremities. In the others they predominantly involved the forearms and lower legs with a characteristic saving of the fingers, causing a symmetric hardening of the skin with stiffness and contractures of subcutaneous tissues (adipose tissue, muscle and joint). In one of these patients (pt 1) the joint and muscle retractions over elbows, hands, knees and ankles were so severe that they caused functional disability and development of infected ulcers with fibrinous bases on the legs.

Four of the 10 patients (pts 5-8) presented with hard discromic alteration evolved in xerotic plaques morphea-like over the abdomen, the chest and the proximal part of the upper and the lower limbs; the skin became irregularly thickened, with depressed areas giving a rippled appearance. Two patients (pts 9-10) presented with small areas of discromic and atrophic patches with an erythematous margin on the trunk, in particular on the cutaneous fold. Only one patient (pt 9) suffered from Raynaud's phenomenon (RP) which developed together with the cutaneous involvement.

Red and white blood cell counts were within reference ranges for all patients, and only 1 patient showed thrombocytopenia (platelet count 90.000/ mm^3). No patient showed elevated transaminase or lactic dehydrogenase levels. Seven patients showed ANA positivity, 5 of them with nucleolar pattern. The typical scleroderma-associated autoantibodies, such as anti-centromere and anti-Scl70, were not detected in any of the cases. No further anti-ENA antibodies, nor anti-DNA antibodies, were found. Findings were positive for anti-smooth muscle antibodies in one patient.

Except for one subject who had a hepatitis B virus infection during the period between HSCT and the development of cGVHD, serologic evaluation for hepatitis B and C viruses, Epstein-Barr virus,

Table I. *Cutaneous manifestations of chronic graft-versus-host disease.*

1. Lichenoid lesions	They represent a prominent part of the initial presentation of cGVHD and sometimes precede the development of a more generalized clinical picture of systemic cGVHD
2. Sclerodermatous lesions	They include: a) severe skin sclerosis and joint contractures resembling systemic sclerosis (SSc) b) eosinophilic fasciitis, a fibrosis disorder related to deep morphea c) benign morphea-like patches of sclerotic skin and atrophy
3. Pigmentation disorders	They comprise areas of hypopigmentation and hyperpigmentation

cGVHD = chronic graft versus host disease; SSc = systemic sclerosis

Table II. *Demographic and clinical characteristics of the patients affected by sclerodermatous chronic graft versus host disease.*

	Age	Sex	Diagnosis	Interval time between HSCT and onset of cGVHD (months)	Skin areas involvement	RP	ANA test	NVC	Involved Organs
Pt 1	26	M	ALL	26	Upper and lower limbs, hands and feet; saving of the trunk	No	1:80 N	normal	NO
Pt 2	61	F	AML	28	Forearms, thighs and legs; relative saving of the trunk	No	1:1280 N	pattern early	*LUNG*: mild obstructive deficiency
Pt 3	41	M	AML	12	Forearms and arms; legs and feet.	No	neg	aspecific microangiopathy	*LUNG*: Mild reduction of DLCO
Pt 4	60	F	AML	10	abdomen, anterior chest,and then hands, arms, legs, feet	No	1:80 S	normal	NO
Pt 5	38	M	AML	36	abdomen and forearms	No	1:320 N	normal	*HEARTH*: Moderate left atrial dilatation; mild pericardium effusion
Pt 6	36	M	NHL	20	Trunk, upper and lower limbs	No	1:80 N	n.d.	NO
Pt 7	52	F	MDS	87	anterior chest, arms and thighs	No	1:80 S	normal	NO
Pt 8	36	M	AML	12	Trunk and arms and thighs	No	neg	normal	NO
Pt 9	38	F	MDS	31	Cutaneous fold on the trunk	Yes	neg	aspecific microangiopathy	NO
Pt 10	37	M	AML	10	Anterior chest, slight thickening at ankles	No	1:640 N	normal	NO

Pt: patient; HSCT: haematopoietic stem cell transplantation; cGVHD: chronic graft versus host disease; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic sindrome; AML: acute myelogenous leucemia; NHL: non-Hodgkin lymphoma; RP: Raynaud's phenomenon; ANA: antinuclear antibodies; N: nucleolar pattern; S: speckled pattern; NVC: nailfold videocapillaroscopy; DLCO: diffusing lung capacity for carbon monoxide

CMV and Parvovirus B19 demonstrated no differences between pre- and post-HSCT results. In particular, no patients had a CMV infection at the time of skin sclerosis. None of the patients had lung fibrosis on chest radiography. Pulmonary function tests demonstrated mild obstructive deficiency in one patient and slight reduction of diffusion capacity for carbon monoxide in another one.

Concerning the heart, a moderate left atrial dilatation with mild pericardium effusion was observed in one patient. No patient had kidney or esophagus involvement. The NVC showed the presence of few giant capillaries and frequent capillary hemorrhages with a well-preserved capillary distribution suggestive of "early-scleroderma pattern" in one subject; in another two cases a non-specific microangiopathy was documented, characterized by mild edema, mild capillary tortuousness, enlarged capillaries and rare hemorrhages, but not giant capillaries.

DISCUSSION

In our study we reviewed 10 cases of sclerodermatous cGVHD, focusing on clinical, instrumental and laboratory resemblance to SSc. Our data showed that none of the patients fulfilled the ACR criteria for SSc (8). Furthermore, neither anti-Scl70 nor anti-centromere antibodies were detected. This is different from other previous experiences reported (6), but in agreement with the report of a case series of 17 patients by Penas et al (2). The cutaneous involvement showed differences in appearance, extent and progression. In 4 of the 10 cases reported, tissue induration involved not only the skin but also deeper structures causing joint contractures. Unlike SSc, our patients with sclerodermatous cGVHD showed none or mild organ involvement; in none of the cases were there lesions resembling those of SSc. Among 9 cases of generalized sclerodermatous cGVHD Penas et al. (2) described frequent involvement of the liver (8 cases) without furnishing more details, but it should be noted that the majority of the patients received a hepatotoxic drug such as azathioprine. NVC showed an "early-scleroderma pattern" in 1 patient; other two subjects, one of them suffering from RP, presented aspecific microangiopathy. Therefore, unlike SSc, in which endothelium is early damaged and vascular alterations are supposed to be a primary event that may drive the fibrotic process, sclerodermatous cGVHD patients rarely suffer from RP and rarely have microvessel alterations. To our knowledge this is the first evaluation of NVC in patients with sclerodermatous cGVHD.

The fibrotic process that is shared by sclerodermatous cGVHD and SSc likely recognizes different initial stimuli, even if the pathways of fibrosis development may be common, as supported by the detection of stimulatory autoantibodies against PDGF receptor in patients with extensive cGVHD as well as in SSc (9-10).

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