Case Report

Nonmyeloablative Stem Cell Transplant in a Patient with Advanced Systemic Sclerosis and Systemic Lupus Erythematosus

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ABSTRACT. Systemic sclerosis (SSc) is an uncommon connective tissue disease characterized by excessive collagen deposition within the skin and internal organs. Most patients with diffuse severe SSc are treated with immunosuppressive agents, but patients with advanced disease have very high 5-year mortality rates despite adequate therapy. We describe a patient with both diffuse cutaneous SSc and systemic lupus erythematosus who showed mixed chimerism 29 months after undergoing nonmyeloablative stem cell transplant. She experienced remission of both diseases. (J Rheumatol 2004; 31:2513–6)

Key Indexing Terms:
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Systemic sclerosis (SSc) is an uncommon heterogeneous connective tissue disease characterized by excessive collagen deposition within the skin and internal organs[1-3]. Although its exact pathogenesis remains unknown, SSc is characterized by T cell activation, autoantibody production, and cytokine release that leads to fibroblast activation, increased collagen synthesis and deposition, microvascular damage, and vascular injury in the skin and internal organs[4]. Although no medications have been found to be effective in the treatment of diffuse severe SSc, immune suppression is frequently considered the best therapeutic option. However, patients with high modified Rodnan skin scores and pulmonary involvement have a 5-year mortality rate of roughly 50% with current treatment modalities[5].

A combination of high dose chemotherapy and autologous stem cell transplant (SCT) has been used in the treatment of various autoimmune diseases including SSc[6,7]. In most cases, this treatment has not produced definitive cures[8,9].

Allogeneic SCT using a nonmyeloablative conditioning regimen is frequently used for allografting in nonmalignant diseases[10]. Recent studies have shown that stable mixed chimerism may be sufficient to induce remission in genetic disorders[10]. Experimental data from animal models have also suggested that lasting remission can be achieved in autoimmune diseases after induction of mixed chimerism with allogeneic cells[11].

We describe a patient with diffuse cutaneous SSc and systemic lupus erythematosus (SLE) who displayed mixed chimerism 29 months after she had undergone nonmyeloablative SCT, with continued remission of both diseases.

CASE REPORT

A 21-year-old woman developed Raynaud's phenomenon in February 1996, followed by progressive diffuse skin thickening involving her proximal and distal extremities, trunk, and face. She also developed dysphagia, digital pitting scars, loss of digital pulp, and telangiectasias involving her face and oral mucosa. In February 1998, SSc was diagnosed. Her modified Rodnan skin score at her first visit to our center in May 1998 was 20. At that time, autoantibody testing was positive for antinuclear antibodies (ANA, in a speckled pattern), antiribonucleoproteins, and anti-Smith (anti-Sm) antibodies. Testing for antibodies to double-stranded DNA (anti-dsDNA), SSA (anti-Ro), SSB (anti-La), and Scl-70 was negative. The results of chest radiography, pulmonary function testing with diffusing capacity for carbon monoxide, electrocardiography, complete blood count with differential and platelet counts, and creatine kinase testing were normal.

Treatment was started with low dose D-penicillamine (62.5 mg/day) and prednisone (2.5–30 mg/day). The D-penicillamine was discontinued in January 1999. Methotrexate (MTX, 10 mg/week) was added in May 1998, but was discontinued in June 1999, when SLE was diagnosed on the basis of encephalopathy, lymphopenia, and thrombocytopenia supported by positive serologic testing for anti-Sm and anti-dsDNA autoantibodies. Azathioprine was started, and the prednisone dosage was increased. Daily oral cyclophosphamide was substituted for azathioprine in March 2000 because of continued disease activity: the skin score worsened and she required the use of a wheelchair. On the basis of this rapid deterioration, her

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young age, and the failure of her disease to respond despite immunosuppressive therapy, we considered nonmyeloablative allogeneic transplant.

At her pretransplant evaluation, she had a modified Rodnan skin score of 33. Complete blood counts and results of blood chemical testing, including creatine kinase, were within normal limits. Antibody testing was positive for anti-dsDNA at 1:126, and for ANA (speckled pattern). Tests for antiribonucleoproteins and anti-Sm antibodies were also positive, whereas tests for anti-La, anti-Ro, and anti-Scl-70 were negative. The erythrocyte sedimentation rate was 50 mm/h and C-reactive protein concentration was 1.57 mg/l.

The conditioning regimen included 15 mg/kg cyclophosphamide and 30 mg/m^2 fludarabine daily for 5 days. Rabbit antithymocyte globulin (5 mg/kg) was administered for one day according to protocol, but the 2 subsequent doses had to be reduced to 3 mg/kg because of infusion-related toxicity. This was followed one day later by infusion of allogeneic peripheral blood stem cells from her human leukocyte antigen-identical brother. The total dose of nucleated stem cells was 4.88×10^8/kg body weight, and the CD34 cell dose was 5.37×10^6/kg body weight. Graft-versus-host disease (GVHD) prophylactic therapy consisted of tacrolimus and MTX. MTX was given at 5 mg/m^2 on Days 1, 3, and 6 after transplant. The patient was maintained on low dose methylprednisolone because of prolonged corticosteroid use.

The early posttransplant period was uneventful except for an episode of respiratory syncytial virus infection on the 81st day that was successfully treated with ribavirin. Neutrophil and platelet engraftment occurred on Days 13 and 19, respectively. Fluorescence *in situ* hybridization chimerism studies performed 3 months posttransplant showed mixed chimerism of 40% recipient cells. She did not develop GVHD, and all her immunosuppressive medications were gradually reduced to discontinuation by about 9 months after the transplant. Table 1 shows the results of chimerism studies.

One hundred days after the transplant, the patient's skin had recovered to nearly normal, and she experienced remission of both SSc and SLE (according to clinical and laboratory criteria). Her modified Rodnan skin score had decreased to 18 and resolved to 1 at 29-month followup (Figure 1). At that followup, she had no dysphagia or muscle weakness and only mild Raynaud's phenomenon, and her quality of life had gradually improved.

She experienced a flare of her SLE in May 2002, which we treated with moderate-dose prednisone, which was then tapered to discontinuation. This may be related to mixed chimerism. At the time of her last clinic visit, in May 2003, she was leading a normal life, attending college fulltime, working parttime, and walking without assistive devices. She currently takes no medications for her SSc or SLE.

Table 2 shows the clinical and laboratory assessments during the followup period of 29 months.

DISCUSSION

Our patient, who had both severe diffuse cutaneous SSc and SLE, was successfully treated with nonmyeloablative stem cell transplant. Because the mortality rate is very high in patients with diffuse SSc and in those younger than 35 years old[12], and because our patient's disease had failed to respond to immunosuppressive therapy, we had few conventional treatment options[13,14].

Table 1. Posttransplant chimerism studies.

Months Posttransplant	Mixed Chimerism Pattern (% recipient cells)	Donor Myeloid Cells, %	Donor T Cells, %
3	40	NA	NA
6	75	27	27
18	92	15	28
29	82	14	15

NA: not available.

In prospective randomized trials of patients with SSc, no therapeutic agent has been shown to increase survival[14]. Treatment with low dosages of immunosuppressive medications such as chlorambucil and D-penicillamine has proved disappointing in clinical practice, and D-penicillamine showed no clear benefits in a prospective controlled trial[15,16].

High dose immunosuppressive therapy followed by autologous stem cell transplant relies on intensive immunosuppression and myelosuppression in the conditioning treatment to "reeducate" the immune system. However, reported responses after autologous transplant for autoimmune diseases have been poor and rarely sustained[17]. Most autologous transplants have been associated with high rates of mortality and relapse[13,18].

Various autoimmune diseases have remitted partially or completely in patients who have undergone allogeneic SCT for other clinical indications[9,19]. After allogeneic transplant, recipient lymphoid cells are eliminated and replaced with donor-derived cells. The hypothesis for this is that the hematopoiesis and immunity derived from the allogeneic donor's cells "resets" the immune system and provides a new T and B cell repertoire that establishes immune tolerance and allows subsidence of the autoimmune disease[20]. Allogeneic hematopoietic transplant has been successful in ameliorating a range of autoimmune diseases in animal models[11,21]. In 4 of 5 evaluable patients with Crohn's disease who underwent allogeneic transplant for concurrent leukemia, the Crohn's disease remained in remission for 18 months to 15 years after the transplant[22]. Chakrabarti, *et al*[23] describe a patient with a history of psoriasis and indolent non-Hodgkin's lymphoma who underwent nonmyeloablative SCT for the lymphoma. Twenty-one months after the transplant, both diseases were in complete remission with stable mixed chimerism (30–40% donor cells) despite substantial recovery of T cell subsets and antigen-specific responses[23]. Nash, *et al*[24] recently reported on 2 patients who underwent allogeneic transplant for treatment of SSc. Both patients experienced significant improvements in their disease status after transplant. In another case report[25] a patient with rheumatoid arthritis who had failed a prior autologous transplant procedure underwent an allogeneic transplant using a nonmyeloablative preparative regimen.

However, the mortality rate for allogeneic SCT is high, in the range of 25–30%. This is primarily related to the development of acute and chronic GVHD after transplant and also an increased susceptibility to infections because of delayed immune reconstitution. Thus, in most cases, the risk has outweighed the potential benefits[26]. Nonmyeloablative preparative regimens have recently been developed to reduce the rate of treatment-related morbidity and

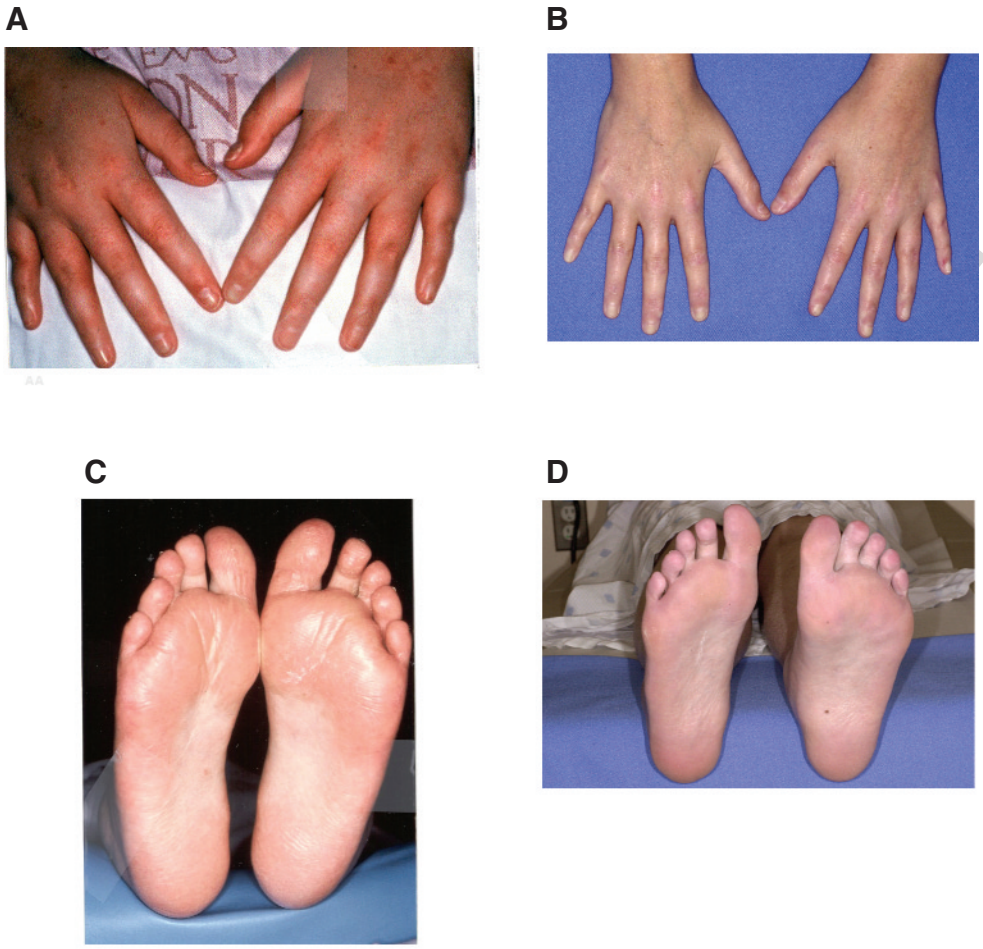

Figure 1. A. Pretransplant: swollen hands, digital pitting scars, and loss of digital pulp. B. Posttransplant: normal hand. C. Pretransplant: sclerosis of the soles. D. Posttransplant: normal soles. E. Pretransplant: sclerosis of the upper thighs. F. Posttransplant: normal skin of the upper thighs.

mortality[27]. Nonmyeloablative preparative regimens are designed to minimize toxicity while providing sufficient immunosuppression to prevent graft rejection. This results in less tissue damage, less cytokine release, and a lower incidence of GVHD[28]. The establishment of stable mixed chimerism confers self-tolerance[29]. Therefore, nonmyeloablative SCT is increasingly being used for allografting in nonmalignant diseases[10].

Table 2. Clinical and immunologic followup of the patient.

			Time Posttransplant, mo			
	At Diagnosis of SSc	Pretransplant Evaluation	3	6	18	29
Modified Rodnan skin score	20	33	18	18	5	1
Range of movement	No contracture	Elbow contracture	No contracture	No contracture	No contracture	No contracture
ANA	Positive	Positive	Positive	Positive	Positive	Positive
Anti-dsDNA	Positive	Positive	Positive	Negative	Positive	Negative
Anti-Ro	Negative	Negative	Negative	Negative	Negative	Negative
Anti-La	Negative	Negative	Negative	Negative	Negative	Negative
Anti-Smith	Positive	Positive	Negative	Negative	Negative	Negative
CRP, mg/l	NA	1.57	NA	NA	3.56	0.82
RNP	Positive	Positive	NA	NA	Positive	Positive

RNP: ribonucleoprotein, NA: not available, ANA: antinuclear antibody, CRP: C-reactive protein.

At 29 months after transplant, our patient's SSc and SLE remained in clinical remission, with a Karnofsky performance status score of 100% and no evidence of chronic GVHD. Considering the normal blood counts and normal anti-Sm antibody titers, we concluded that she was free of clinically significant autoimmune disease.

Nonmyeloablative transplant may be a new option for effectively eradicating resistant, self-reactive lymphocytes without the need for myeloablative conditioning, as has also been recommended for patients with other indications for allogeneic transplant[30]. The use of myeloablative conditioning in conjunction with autologous or allogeneic SCT was recently recommended in a consensus report issued by an international committee of rheumatologists and bone marrow transplant specialists[31]. Nonmyeloablative conditioning may accomplish the same goal with less toxicity and thus may be more desirable. It is an option that should be studied further, especially in those patients with advanced SSc and other autoimmune diseases who have a suitable donor available.

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