Scleroderma: The Need for Extreme Remedies

UT Southwestern Medical Grand Rounds

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Case Presentation:

The discussion today will be focused on the case of Mr. A. He is a 34-year old man who has had Raynaud's syndrome since his teen years, and who was diagnosed with scleroderma in 2005. He recalls that his Raynaud's was rather severe when he was in high school in Michigan. He was evaluated at the University of Michigan Medical Center in Ann Arbor and was treated with calcium-channel blockers including nifedipine. He had no digital ulcers at that time and apparently no skin changes were noted. He subsequently entered the Marines and was stationed in California where the warmer weather did not cause any significant problems with his hands. During his period of service, geopolitics focused US military attention on warm weather areas of the world, and he never did any Arctic training or deployments.

After he left the service and moved to Texas, when he was about 28, he noted increasing heartburn and stomach problems. He underwent a gastrointestinal evaluation and was treated for esophagitis with proton pump inhibitors. During this time the problems with cold digits worsened and he developed a sore at the tip of one of his index fingers. At first he thought he had something in the finger, like a splinter, but it subsequently became apparent that it was something more serious. The gastroenterologist suggested that he needed further evaluation for possible scleroderma, and he was referred for rheumatology and pulmonary consultations.

He has otherwise an unremarkable medical history. He has never had problems with blood pressure or renal function. He is a nonsmoker who is married and has one child. He works in administration at a local college. His avocations include bike riding. His family history is positive for pulmonary hypertension in his grandmother; this history has been carefully researched and verified by other family members. However, he is not aware of anyone in his family with scleroderma, lupus or rheumatoid arthritis.

His manifestations of scleroderma have included telangiectasias, mostly on the face, skin tightening on his hands and digital ulcerations, in addition to the esophageal problems. His serologic evaluations in our clinics show positivity for the anti-RNP autoantibody, but other autoantibodies including those directed against Scl-70 (topoisomerase-I), centromere, SSA and SSB (the Sjogrens antibodies) and Sm (specific for lupus) have all been negative. There is no record of ANA testing in our medical chart.

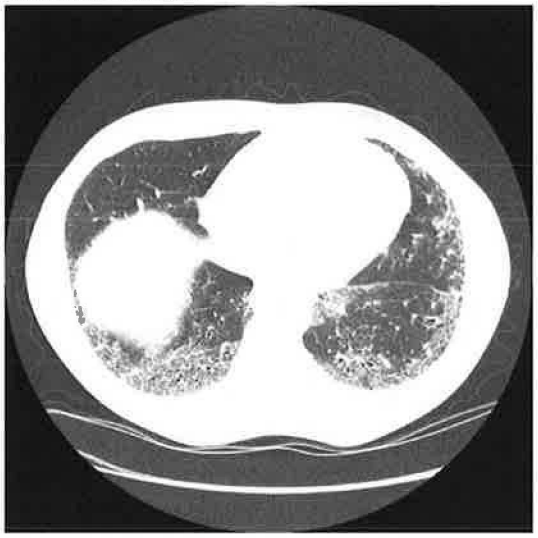


Figure 1 *High Resolution CT of chest, 2005.*

He was evaluated for dyspnea by Dr. Glazer in our pulmonary clinic. PFTs showed restrictive changes and diffusion impairment without evidence of pulmonary hypertension. Imaging studies showed honeycombing and ground glass changes as well as traction bronchiectasis (Figure 1). For treatment of the lung problems, in 2005 he had a 6-month course of monthly intravenous cyclophosphamide, utilizing the standard lupus nephritis protocol. Following completion of this treatment course, which he tolerated without problems, he was placed on maintenance therapy with mycophenolate mofetil, 2000 mg daily, and low-dose prednisone, which is currently at a dose of 10 mg/day. He has in recent months noted decreased problems with shortness of breath and is considering taking up bicycling again with the return of warmer weather.

A major problem throughout his illness has been digital ulcers. About a year ago, during the last winter, he developed numerous painful ulcerations. The pain became so severe, despite use of hydrocodone, that he required fentanyl patches every 48 hours. He wore gloves much of the day, had a heater in his office and had difficulty with daily activities like using the computer keyboard. Treatment with nifedipine was obviously insufficient at this point, and he was started on bosentan. Because this medication is only FDA-approved for treatment of pulmonary hypertension (which he does not have) and not for digital ulcers, insurance coverage was initially a problem preventing him from at times getting this medication. However, this eventually resolved so that he could get regular refills. Despite this treatment, ulcers on his fingers worsened to the point of gangrenous change in two digits of the left hand. He was referred to Dr. Mezera in orthopedics for consideration of selective digital sympathectomy and in June 2009 he underwent this procedure on digits 2 through 5 of the left hand. He had no problems healing from the procedure. He noted slow improvement in fingers on both hands, and over the past 2 months he has had closure of all ulcers and healing with autoamputation of gangrenous changes. He has now weaned himself off fentanyl.

History of scleroderma:

The title of this grand rounds is taken from an aphorism of Hippocrates and it is possible he first described this disorder in Athens more than 2 millennia ago. However, the first formal case report is generally credited to a physician in Naples Italy, Carlo Curzio, who in 1752 published a monograph in which he described a 15 year old girl with hardening of the skin and decreased mobility of joints. There has been much speculation that in fact this girl did not have scleroderma, in part because he did not describe anything that sounded like Raynaud's syndrome, which is an almost a universal finding in scleroderma. In addition, the patient was described as showing resolution of most abnormalities over the next year, after treatment with warm baths and warm milk. Reversibility of scleroderma with any therapy is not usually observed, so this further calls into question the accuracy of the diagnosis in this early case.

The painter Paul Klee was one of the more notable individuals who suffered from scleroderma. Klee was Swiss, spent most of his productive life in Germany and then returned to Switzerland prior to his death in 1940. Some of his art, notably the painting known as "The Captive" is thought to reflect the scleroderma sufferer as being held captive in the tight bonds of his own skin. A Klee self-portrait seems to reflect the classic scleroderma facial changes. An interesting review on this subject by Dr. John Varga, a rheumatologist at Northwestern University discusses the interplay of art elements and illness relationship Klee's work [1].

Epidemiology:

Who gets scleroderma? A review article published in 1954 notes that it "is not a common disease nor is it rare" which is an accurate, if not exactly quantitative, assessment [2]. Data collected more recently in a registry started by Dr. Maureen Mayes in Detroit estimated a prevalence of 242 cases per million adults [3](Table 1). The average age at onset was 46 years, 84% of patients were female and 72% were white. By comparison systemic lupus erythematosus, also a relatively rare disorder, has an estimated prevalence of 400-500 cases per million adults, making it about twice as common as scleroderma [4, 5]. The mean age of onset for lupus is younger, 32 years, and the female predominance, 93%, is more striking. In addition, the registry data suggest that lupus has a higher proportion of African-American patients than scleroderma.

Table 1: Demographic Features of Scleroderma and Systemic Lupus

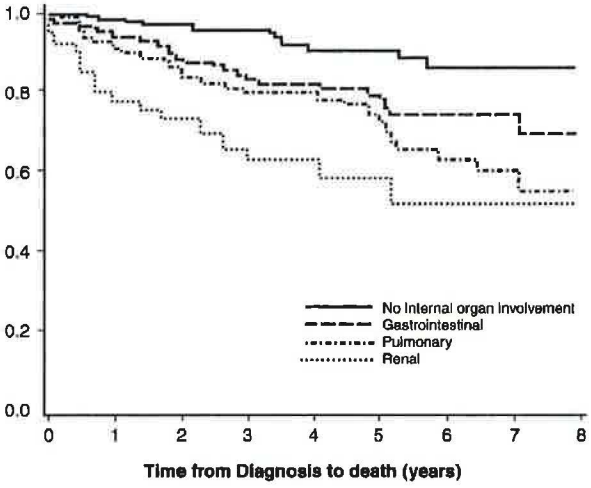
Feature	*Scleroderma*	*Lupus*
Prevalence/million adults	242 cases	400-500 cases
Age at diagnosis	46 ± 15 years	32 ± 13 years
Female	84%	93%
White	72%	56%
African-American	26%	39%

The mortality rate in scleroderma is significantly higher than expected. The Detroit registry data collected in the 1990's suggested that 50% of scleroderma patients are no longer alive 10-15 years after diagnosis (Figure 2). By contrast, systemic lupus erythematosus, a disease that previously had a similar dire prognosis, now has a much higher rate of survival, with 80% of patients alive 20 years after diagnosis.

***Figure 2**: Probability of survival in patients with scleroderma compared to expected survival in a control cohort. (from Mayes et al, 2003; [3]).*

When scleroderma was discussed by Dr. Hugo Jasin in these grand rounds in 1982, the primary cause of death was renal crisis and subsequent renal failure [6]. Scleroderma registry data for the period 1985-1992 show that mortality from both pulmonary and renal involvement were similar [7] (Figure 3). However, with the advent of highly effective treatments for controlling hypertension, notably drugs that block the angiotensin converting enzyme system, pulmonary failure has become a much greater concern than renal crisis.

***Figure 3**: Causes of death in scleroderma patients defined by organ involvement. This analysis was in female patients only (Mayes 2003; [7]).*



There are many ways to look at pulmonary involvement. If patients with lung fibrosis are excluded, the 3-year survival rate is 91% with equal numbers of deaths due to scleroderma-related and scleroderma-unrelated causes [8]. Of the patients with scleroderma-related deaths in this analysis, most were due to either pulmonary hypertension or new onset pulmonary fibrosis in the period of study (Table 2). Less than 10% of the scleroderma-related deaths were due to renal crisis. It is interesting to note that in the non-scleroderma-related death group, infection

and vascular events were less common than cancer, which stands in contrast to the predominance of vascular and infectious deaths in patients with rheumatoid arthritis. The presence of pulmonary fibrosis in scleroderma is also associated with high rates of mortality and in one small study of 22 patients with biopsy-proven fibrosis only 50% were alive at 8 years of followup [9]. These data clearly underline the need for new and aggressive approaches to pulmonary manifestations of scleroderma.

***Table 2**: Causes of death in scleroderma, excluding patients with pulmonary fibrosis at time of enrollment; followup period of 3 years. (Hachulla et al 2009; [8].)*

Causes of Death, N (%)	All Patients (N=546)
Total number of deaths	47 (8.6)
Scleroderma-related deaths	24 (4.4)
• PAH	17
• Pulmonary Fibrosis	2
• Gastrointestinal	2
• Renal crisis	3
Non-scleroderma-related deaths	23 (4.2)
• Cancer	8
• Infection	4
• Cardiovascular/cerebrovascular	2
• Other	2
• Unknown	7

Etiology:

The cause of scleroderma is unknown. However, it does help to consider disease classification as an approach to understanding pathophysiology. Along these lines, the first logical question to answer is whether or not scleroderma is an autoimmune disease. (Table 3).

Table 3: Is Scleroderma an Autoimmune Disease?	
Yes	***No***
Seen in rheumatology clinic	Not helped (hurt) by prednisone Rx
Associated with many autoantibodies	Fibrosis predominates over inflammation
Shares risk genes with lupus	Vascular changes are widespread

Since rheumatologists largely care for these patients, along with other subspecialists, it appears reasonable to answer this question affirmatively. However, this is an operational rather than a scientific definition of autoimmunity and other more objective data in support of this association can be found. The first is that scleroderma is associated with a large number of autoantibodies. Over 75% of scleroderma patients have antinuclear antibodies (ANAs) and subsets of patients show other more specific profiles. Anti-centromere antibodies are present in about 30% of scleroderma patients, largely those who have more limited skin involvement. A separate subset of 30% has antibodies to topoisomerase-I (Scl-70), and these patients are more likely to have extensive skin involvement [10].

Newer information in support of the autoimmune pathogenesis of scleroderma is derived from genetic associations with the disease [11, 12]. It has been recognized for many years that multiplex autoimmune families may have members with scleroderma and other autoimmune diseases, suggesting some common genetic contribution. More recently, large scale genetic studies in scleroderma have identified candidate susceptibility genes that also appear on lists of genes that are associated with lupus, the prototypical autoimmune disorder. These genes include specificities in the HLA Class II locus, some of which show significant correlations with specific autoantibody profiles in scleroderma patients. Other genes that are implicated in both disorders include many that are important to lymphocyte function including BANK1, IRF5 and STAT 4.

Although immune dysfunction appears to be a significant part of scleroderma, other features of the disease raise questions about the role of autoimmunity in pathogenesis. The first is that treatment with glucocorticoids is not usually effective. Even more remarkable is the evidence that glucocorticoids may actually worsen the disease. This is inconsistent with clinical management of most if not all other autoimmune disorders. The evidence for harmful effects of glucocorticoids is derived from the longstanding Pittsburgh registry started by Dr. Virginia Steen, who is now at Georgetown University [13]. Using a case-control approach, 110 pairs of scleroderma patients were identified who were discordant for renal crisis but who were otherwise similar. The glucocorticoid treatment status of each pair was then examined, using four categories:

1. New treatment with high-dose prednisone, defined as 15 mg/day or greater
2. New treatment with low-dose prednisone, less than 15 mg/day.
3. Continuous treatment, meaning that the patients were on prednisone and the dose was not changed at the time of renal crisis.
4. Use of any prednisone, regardless of dose or duration of treatment.

This analysis showed a significantly elevated risk of renal crisis associated with the new institution high-dose prednisone, with an odds ratio of 4.37 and a 95% confidence interval of 2.03-9.43 (Table 4). Furthermore, treatment with any dose or duration prednisone also showed a significant association with renal crisis,

generating a corresponding OR of 3.21 (1.76-5.85). Reasons for the association between glucocorticoids and renal crisis remain obscure. However, an important clinical implication is that high-dose steroids should be used with caution in a seriously ill patient with multiorgan abnormalities and renal failure if there is any suggestion that scleroderma might be the diagnosis. Examination of the blood smear for microangiopathic changes is useful in such a situation, since the absence of these abnormalities makes scleroderma renal crisis highly unlikely.

Table 4: *Case-control retrospective analysis of 110 scleroderma patients with renal crisis vs 119 matched patients without renal crisis (Steen & Medsger 1998; [13].)*

CS Dose	***Case + Control+***	***Case + Control-***	***Case- Control+***	***Case – Control-***	***OR (95% CI)***
New High dose	5	35	8	62	4.37 (2.03-9.43)
New Low dose	3	15	8	84	1.87 (0.79-4.24)
Continuous	1	9	8	92	1.12 (0.43-2.9)
Any	21	45	14	30	3.21 (1.76-5.85)

Another argument against an immune or autoimmune pathogenesis of scleroderma is derived from examination of pathologic changes in the involved organs. Biopsies of involved skin typically show collagenous fibrosis with minimal inflammatory infiltrates. Furthermore, renal changes are most predominant in vessels, which show luminal narrowing and circumferential fibrosis, again with minimal inflammatory change. By contrast the classic renal lesion in systemic lupus erythematosus is highly inflammatory with large numbers of infiltrating leukocytes as well as deposition of antibodies and complement in the involved glomerulus.

The idea that scleroderma revolves around abnormal vasculature is not new and was actually promulgated by Dr. Walter Norton more than 30 years ago, based on discoveries he made while he was a fellow here at UT Southwestern under Dr. Morris Ziff. His data included careful histologic and ultrastructural analyses of involved tissues in which he was able to clearly demonstrate qualitative and quantitative vascular abnormalities. He proposed that scleroderma should be classified as a vascular disease and that the primary site of injury was the capillary bed [14].

Pathogenesis:

The accumulated data suggest that scleroderma involves both immune and vascular abnormalities and results in fibrosis. A central question then, is how do these components interact to cause disease?

One hypothesis of pathogenesis that ties together these different factors is that early events take place in localized areas of ischemia in tissues affected by the vascular hyper-reactivity of Raynaud's phenomenon (Figure 4). This takes into account the usual scenario such as the one presented today in which the vascular reactivity precedes systemic problems by many years. A consequence of repeated bouts of localized ischemia is vascular injury including apoptosis of endothelial cells. Mediators released by damaged endothelium include endothelin-1, cytokines and growth factors. These soluble molecules begin a cascade of other events including increased vascular permeability and leukocyte recruitment. Further downstream from these events, profibrotic changes accumulate resulting in accumulation of collagen in target tissues. Emerging data including results of clinical interventions that will be discussed subsequently suggest that the fibrosis which develops is not necessarily as fixed as it appears, but is dependent on continued immunologic disturbance. This dynamic relationship implies that at least some of these changes may be more reversible than previously thought.

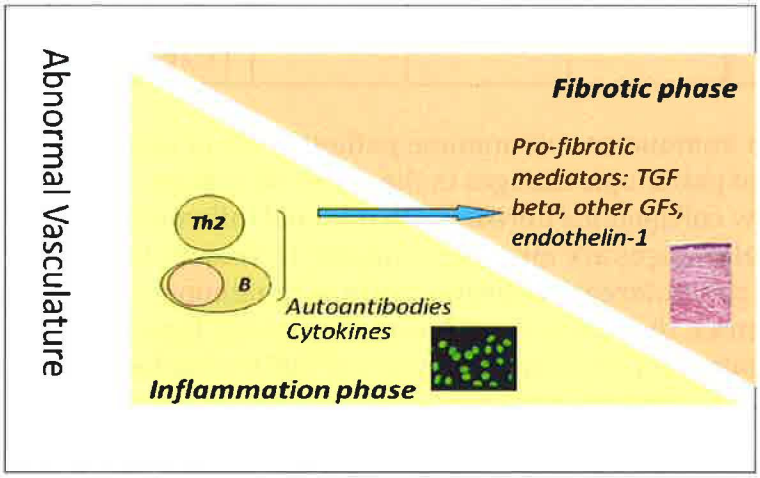


Figure 4: *Pathogenesis of scleroderma postulating underlying abnormal vasculature upon which inflammatory and fibrotic phases develop.*

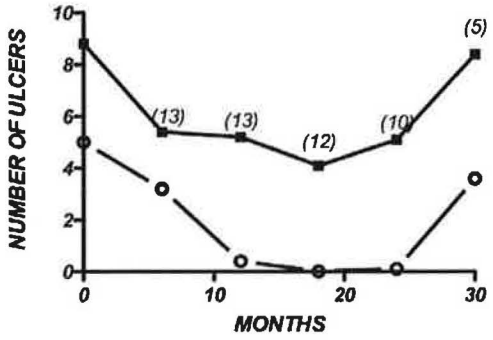
Treatments:

Raynaud's syndrome and digital ulcers: The list of treatments presented by Dr. Jasin in 1982 included such physical interventions as arm twirling and hyperbaric oxygen and psychological strategies such as hypnosis and biofeedback. Drug therapies included adrenergic and alpha blockers as well as smooth muscle relaxants. The relatively new drug captopril was listed in the category of "other" treatments. In 2010, some of these treatments remain in the list including biofeedback to raise the finger temperature, which is something our patient today did try. Sympathectomy is still used but as a selective digital approach rather than at the ganglion level.

Nitrates including topical nitro paste are useful for Raynauds, but as shown by our patient today, this can be insufficient in severe cases with ulceration. Calcium channel blockade is now first-line therapy.

In severe and resistant cases, more intense treatment is needed and that is where the blockade of endothelin-1 becomes important. It is notable that endothelin-1 is possibly the most potent vasoconstrictor yet identified. Although interaction of endothelin-1 with receptors on endothelium can relax the vessel via release of nitric oxide, the constricting effects on smooth muscle cells appear to predominate. Furthermore, the high levels of circulating endothelin-1 in scleroderma patients contribute to fibrosis and vascular remodeling. Bosentan acts to block both types of endothelin receptors and has been shown in controlled clinical trials to prevent development of new ulcers. What was less clear from those trials was whether bosentan could promote healing of digital ulcers. At least one small uncontrolled observational study suggests that healing of ulcers does occur in patients treated with bosentan (Figure 5), and it is a likely factor in the healing of ulcerations observed in Mr. A [15].

Figure 5: Effects of bosentan treatment in scleroderma patients with digital ulcers followed for up to 3 years on therapy. Fifteen patients evaluated at baseline; numbers of patients available for analysis at each time point shown in parentheses. Number of ulcers shown by closed squares; number of healed ulcers shown by open circles. (de la Pena-Lefebvre et al, 2008; [15].



Selective digital sympathectomy is generally reserved for severe cases with threatened loss of digits despite medical intervention. The procedure is done under general anesthesia using a microscope to visualize vascular innervations that are then physically separated from the blood vessel. Improvement in both hands following unilateral surgical intervention, as observed in the present case, has been anecdotally reported and suggests a role for central neuroregulatory signals that improve the vasoconstriction in the contralateral hand [16]. One review of published cases suggests that healing of ulcers after the procedure may take up to 7 months, which is consistent with results we observed [17].

Pulmonary fibrosis: Lung involvement is a major cause of premature mortality in scleroderma, and treatment options for this complication remain somewhat limited. Since inflammation, documented by biopsy or bronchoalveolar lavage, is present in at least a subset of patients with pulmonary fibrosis, treatment with major

immunosuppressants like cyclophosphamide has been advocated. A formal placebo-controlled trial with 1 year of treatment at a maximum dose of 2 mg/kg/day did show a statistically significant improvement in pulmonary function in the cyclophosphamide patients at the end of the treatment period [18]. Both FVC and TLC components of pulmonary function testing were significantly improved. Some additional improvement was observed in the 6 months after treatment was stopped . However, by 2 years, the cyclophosphamide group was not significantly better than placebo-treated patients (Figure 6) [19]. This result suggests that induction of a response with cyclophosphamide should be followed by a maintenance course of a less toxic drug such as mycophenolate mofetil or azathioprine. Several groups have reported success with such an approach, which parallels what was used in the case described today [20].

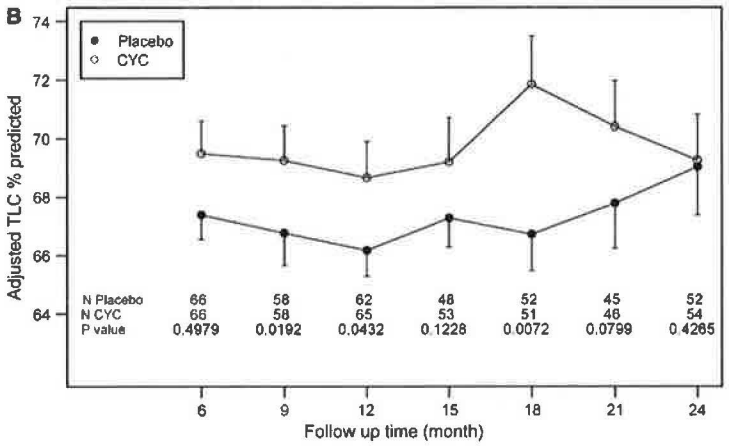


Figure 6: *2-year outcomes for patients enrolled in the Scleroderma Lung Study. Patients were treated with cyclophosphamide or placebo for 1 year and evaluated at 2 years. (Tashkin et al 2007; [19]).*

Stem cell transplantation:

Allogeneic stem cell transplantation: A significant number of patients with scleroderma have progressive organ damage despite available therapies. Treatments that have been advocated for these patients include stem cell transplantation. Data in support of a role for this maneuver can be traced to an analysis of results of allogeneic bone marrow transplants in patients who had coexisting autoimmune disorders at the time that transplantation was done for other indications, usually malignancy or bone marrow failure. Examination of the transplant registry at the Fred Hutchinson Cancer Research Center in Seattle for the two decades from 1969-1989 revealed that there were 13 patients who had autoimmune disorders at the time of the transplant procedure (Table 5) [21]. These pre-existing autoimmune diseases included lupus, rheumatoid arthritis, type 1 diabetes, autoimmune thyroid disease, dermatitis herpetiformis, vasculitis and Crohn's disease. During the followup period, which ranged from 7-20 years, none of these patients had a recurrence of autoimmune disease. The mechanism

responsible for eliminating autoimmunity by replacing stem cells is not known, but these findings in human patients have been corroborated in various animal models.

Table 5: Pre-transplant autoimmune diagnoses in 13 patients undergoing allogeneic SCT at Fred Hutchinson Cancer Research Center 1969-1989

Diagnosis	Number of patients
Rheumatoid arthritis	1
Discoid or systemic lupus	2
Type I Diabetes mellitus	3
Hyperthyroidism	4
Dermatitis Herpetiformis	1
Vasculitis	1
Crohn's disease	1

From Nelson et al, 1997; [21]

Autologous stem cell transplantation: Although there were no scleroderma patients in this cohort, interest in using transplantation for this disease was high because unlike other autoimmune disorders on this list (Table 5), many scleroderma patients are without satisfactory treatment options. It was decided to use autologous rather than allogeneic stem cells because of the lower morbidity of the procedure. A multicenter pilot study was organized and patients were enrolled at five US centers [22]. Inclusion criteria included duration of the diagnosis of up to 4 years (symptoms could have been present prior to the specific diagnosis) and a Rodnan skin score of 16 or greater, consistent with diffuse skin disease. In addition, involvement of a major organ, either lung, kidney or heart was required. All patients had failed immunomodifying treatments (median of 2 drugs failed). The intent of the inclusion criteria was to identify patients with a predicted 5-year mortality of 50% using therapies available in 2002. The profile of enrolled patients included an average age of 41 years, and an average Rodnan skin score of 30. Significant functional disability was indicated by the average baseline score on a modified health assessment questionnaire of 1.88 (on a 0-3 scale). The majority of patients were positive for ANA and about a third had expression of Scl-70 antibodies. All 34 enrolled patients had significant lung disease. The transplant procedure utilized autologous peripheral CD34+ cells that were mobilized using GCSF. Preparation for transplant included total body radiation (with lung shielding in the later patients), cyclophosphamide, high dose prednisone and antithymocyte globulin.

Of the 34 enrolled patients, 27 survived the first year and were evaluable for response to the treatment. Most striking in the 8 year followup analysis was the decrease in Rodnan skin score (Figure 7) ($P<0.001$). This result was confirmed with serial tissue biopsies in selected patients, which documented decreased fibrosis in skin tissues. In addition to the skin changes, functional status as

measured by the modified health assessment questionnaire, was significantly improved over the followup period (P<0.001). Other measures of organ status including pulmonary function and DLCO, serum creatinine and cardiac ejection fraction were essentially unchanged after 5 years. The fact that there was no worsening in other systems was interpreted as a positive outcome. Adverse events included viral and bacterial infections as well as one fungal skin infection. Deaths were due to various causes including renal crisis and respiratory failure. Most of these occurred within 6 months of the transplant; only one death, attributed to myelodysplastic syndrome occurred late, at more than 6 years post-transplant. The overall estimated probability of survival at 5 years was 64%.

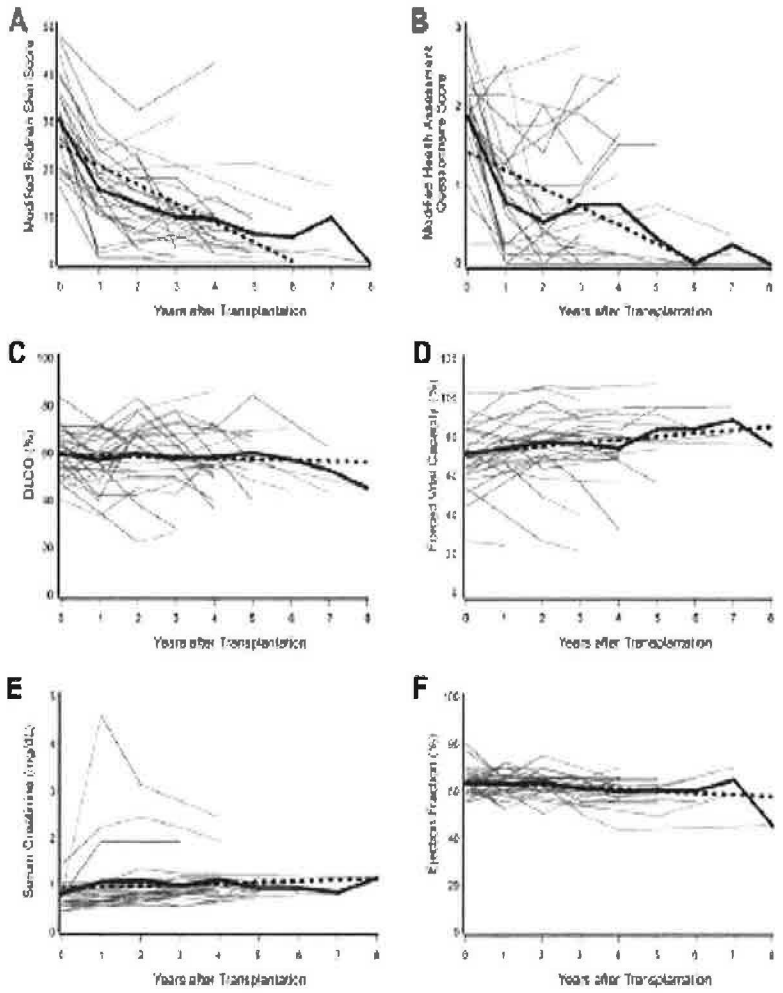


Figure 7: *Outcomes in scleroderma patients treated with high dose immunosuppressive therapy and autologous stem cell transplantation. Black line represents mean values; broken line indicates estimated linear relationship over time.*
P values: panels A and B <0.001; panel C=0.50; Panels D and E =0.01; panel F = 0.04. (Nash et al 2007; [22]).

The results of this trial served as the impetus for organizing a randomized study comparing autologous stem cell transplantation to high dose cyclophosphamide. This ongoing NIH-sponsored trial is entitled "Scleroderma: Cyclophosphamide or Transplantation" and uses the acronym SCOT. The design of this study is based on the concept of equipoise between the two treatments and patients who agree to

randomization must be prepared to accept either treatment assignment. The SCOT study has an informative website that includes patient testimonials and study locations (www.sclerodermatrial.org). We tried for about a year to enroll patients at UTSW but had problems finding individuals who fit the criteria; basically this requires a very ill patient who nonetheless is not too ill to undergo the procedure. At the present time, more than 60 patients have been randomized into SCOT and enrollment is continuing. Patients from our area who are interested can be evaluated by Dr. Maureen Mayes in Houston, which is the site that is closest to Dallas. The actual transplant procedure will take place at MD Anderson Hospital.

Summary:

Scleroderma remains one of the most difficult diseases that we encounter in medical practice. Although new therapies have improved many aspects of outcome, a significant proportion of patients are not satisfactorily controlled with available treatments, and premature death remains a too-common outcome. Nevertheless, it is clear that advances have been made since this topic was discussed in these grand rounds more than 27 years ago. Renal crisis is a far less common event due in large part to the use of ACE inhibitors. Drugs like bosentan have improved significantly the treatment of digital ulcers. A more aggressive approach to interstitial lung disease using the concept of induction and maintenance immunosuppressive therapies can at least stabilize this process in many patients. Whether interventions like stem cell transplantation might offer hope to those failing currently available treatments remains to be clearly demonstrated, but it is encouraging that this is being carefully evaluated in a randomized trial. Also encouraging and somewhat surprising is the fact that the pipelines of many pharmaceutical companies include numerous products in various stages of development for scleroderma. This has been fostered in part by the orphan status of drugs for the indication of scleroderma.

Registries: Patient registries have contributed significantly to the development of insights about scleroderma. Some findings have changed therapies, like the avoidance of prednisone in renal crisis, while others have opened up new areas of interest, like stem cell transplantation. Three such registries focused on autoimmunity, scleroderma or related disorders are located either here at UTSW or in Houston and are enrolling individuals to help further these kinds of discoveries. Descriptions and contact information for these registries are provided on the following page.

- **Dallas Regional Autoimmune Disease Registry (DRADR)**
  - Location: UTSW
  - PI: Dr. David Karp
  - Coordinator: Valerie Branch
  - Enrolls autoimmune and suspected autoimmune disorders, family members and healthy controls.
  - Contact information: 214-648-2018

- **Scleroderma Family Registry and DNA Repository**
  - Location: UT Houston
  - PI: Dr. Maureen Mayes
  - Coordinator: Marilyn Perry
  - Enrolls scleroderma patients and family members
  - Travel to Houston is not required
  - Contact information: 1-800-736-6864; sclerodermaregistry@uth.edu

- **Morphea Registry and DNA Repository**
  - Location: UTSW
  - PI: Dr. Heidi Jacobe
  - Coordinator: Stephanie Saxton
  - Enrolls morphea patients 3 years of age or older
  - Travel to UTSW is not required
  - Contact information: 214-645-8973
  - Google "Morphea Registry"

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