Long-Term (22 Year) Successful Treatment of Limited Systemic Scleroderma Using Plasmapheresis

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Abstract

While a number of studies have shown short-term beneficial effects of plasmapheresis (PA) for treating systemic scleroderma (SSc), there have been no reports on the very long-term usage of PA as the sole systemic treatment intervention. We report on the case of a male patient, originally diagnosed with limited systemic scleroderma (lcSSc) in early 1990, who has been undergoing regular plasmapheresis treatments for more than 22 years, beginning in late 1993. Prior to commencing treatment, the patient exhibited symptoms including severe gastroesophageal reflux disease (GERD) with esophagitis, frequent Raynaud’s attacks, reduced lung function, and chronic chilling. With the exception of mild residual Raynaud’s, all of the patient’s symptoms reversed after three years of regular PA treatments and he remains in complete remission. While the typical explanation for the therapeutic benefits seen with PA focuses on temporary reduction of circulating antibodies or other potential pathogenic factors, we propose instead an alternative explanation based on a novel disease pathogenesis model for SSc.

Introduction

Systemic scleroderma (SSc) is a rare autoimmune disease that primarily affects middle age women. There are several different variants of SSc, with the most common forms being diffuse cutaneous systemic scleroderma (dcSSc) and limited cutaneous systemic scleroderma (lcSSc). It is disabling, disfiguring, and steadily progressive, attacking internal organs through fibrotic processes in addition to its characteristic skin changes. Because of these fibrotic processes, there are no periods of remission with SSc, unlike other autoimmune diseases such as lupus or rheumatoid arthritis.

Current treatment approaches focus on using immunosuppressants to slow the disease process plus interventions targeted at specific symptoms. Neither approach is currently very effective.

Case History

We report on the case of a 68-year-old male, diagnosed in 1990 at age 43 with lcSSc. When seen initially in January 1990, the patient complained that he had developed Raynaud's symptoms beginning in 1985, with increasing severity over the intervening years. Upon initial examination, the patient complained that his fingers were slightly swollen in the mornings and that he was experiencing finger stiffness as well. Lab tests done at that time demonstrated a positive antinuclear antibody titer of 1:1280 with centromere pattern. A later (7/6/90) anti-centromere antibody test was positive at a titer of 1:2560. These lab results,
combined with severe Raynaud's and other related clinical symptoms, lead to a diagnosis of early stage lcSSc (then called CREST syndrome).

Over the next four years, the patient's symptoms progressed rapidly. Following a complaint of increasing GERD, an upper endoscopy was performed on May 21, 1991 that showed erosive esophagitis. The patient was placed on omeprazole for the GERD and nifedipine for the Raynaud's symptoms.

By late 1993, the patient was on 40mg omeprazole BID with poor control of GERD symptoms, complained of chronic severe chilling as well as increasingly severe Raynaud's symptoms. While minor nailbed capillary enlargement was visible upon physical exam, there was no evidence of skin changes, calcinosis or telangiectasias. A baseline pulmonary function test (PFT) performed on 7/7/94 showed significantly reduced diffusing capacity of the lungs for carbon monoxide (DLCO/VA) at 68% of normal. Low DLCO is a risk factor for later development of pulmonary hypertension, which has a poor prognosis in lcSSc. In October 1995, the patient complained of persistent irregular heartbeats. An echocardiogram performed on 2/3/97 showed trace mitral and tricuspid regurgitation. A stress echocardiogram performed on 3/20/95 was negative for ischemia, although he did exhibit frequent premature atrial contractions (PACs).

After receiving approval for insurance coverage of a one-year trial of PA, the patient began to receive regular PA treatments in November 1993. The protocol used at the beginning was one volume exchange of 5% albumin, administered one treatment per week for four weeks. This was followed by a two-month interval with no treatments. This pattern was then repeated for a total of 16 treatments during the first year.

After one year, the patient reported improvement in GERD (symptoms well-controlled by 40mg omeprazole QD), improved Raynaud's but still a problem in cold weather, and reduced chronic chilling. A repeat PFT performed on 5/31/95 showed that DLCO/VA was stable at 69% of predicted. Because the patient's symptoms showed no progression and there appeared to be early evidence of symptom improvement at the end of the one-year trial period, the approved trial period was extended one additional year, using the same protocol as before.

At the end of the second year of treatments (32 treatments), GERD symptoms were well-controlled by 20mg omeprazole QD (see note below), Raynaud's improved to mild even in cold weather, nailbed capillary enlargement resolved, DLCO improved to 76% of predicted, and he had a normal upper endoscopy. (Note: the patient attempted to stop the omeprazole but symptoms returned. We eventually realized that this was a rebound effect and the patient tapered off omeprazole over a 3-month period and has been completely free of GERD symptoms since 1998).

A PFT performed on 1/16/96 indicated that DLCO/VA had returned to normal. A routine exam performed on 3/31/98 showed no evidence of continuing PACs.

In order to determine if continued PA was necessary to sustain symptom improvements, on 12/5/96, PA treatments were suspended to observe the natural progression of the disease. Approximately six months later, the patient again complained of reflux symptoms. PA treatments were resumed on the previous schedule beginning 6/19/97. The patient complained of reduced but continuing reflux symptoms six months after resuming treatments. At one year after resumption of treatments (16 treatments) all reflux symptoms had again disappeared. Notably, a second attempt to alter the treatment protocol was tried several years later. Over a
two-year timeframe, the inter-treatment interval was gradually increased from 8 ½ weeks to 11 weeks, at which point reflux symptoms again began to re-occur. The original treatment protocol was restarted and reflux disappeared about six months later.

One notable change in laboratory measures occurred that appears to be treatment related. Table 1 shows the patient’s erythrocyte sedimentation rate (ESR) levels beginning about two years after diagnosis. The initial level (13 mm/h) is near the top end of the normal range for ESR (0 to 15 mm/h). After 12 treatments over a nine-month period, the patient’s ESR dropped markedly to 10 mm/h. This trend continued so that after about a year and half of treatments (28 total), the ESR had reduced to 6 mm/h. Ultimately, the ESR stabilized at 4 mm/h and has remained at that level ever since. The potential significance of this reduction in ESR over time is discussed below.

<table>
<thead>
<tr>
<th>Date</th>
<th>ESR (mm/h)</th>
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<tbody>
<tr>
<td>11/20/91*</td>
<td>13</td>
</tr>
<tr>
<td>Post-Treatment</td>
<td></td>
</tr>
<tr>
<td>9/13/94</td>
<td>10</td>
</tr>
<tr>
<td>6/23/95</td>
<td>6</td>
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<tr>
<td>8/27/03</td>
<td>4</td>
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<td>11/9/06</td>
<td>4</td>
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<td>6/18/09</td>
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The patient is currently in excellent physical condition (he indicates that he exercises at least 2 hours per day) with no known residual symptoms of limited scleroderma except persistent mild Raynaud's. He currently has no other significant health issues. All labs are within normal limits.

Discussion

A series of research studies [1,2,3,4,5] published between 1975 and 2006 have consistently shown abnormally elevated blood viscosity in the majority of systemic scleroderma patients. The specific type of blood hyperviscosity documented in these research articles (when reported) is increased red blood cell (RBC) aggregation. Notably, increased plasma viscosity and RBC aggregation is normal in patients with primary Raynaud's (not related to an underlying autoimmune disease) but significantly increased (p<.001) in patients with Raynaud's secondary to SSc [6]. PA (also referred to as therapeutic plasma exchange or TPE) is considered to be the "gold standard" for treating a number of different hyperviscosity syndromes. Research indicates [7] that each PA treatment reduces blood viscosity by 20% to 30%.

PA has been tried with SSc patients since 1978, both individually and as part of small pilot studies [e.g., 8,9,10]. The usual rationale offered in these studies for trying PA (as well as the post hoc explanation for the benefits seen) is the presumption that some circulating factor is involved in disease pathogenesis, e.g., autoantibodies or immune complexes, or other substances such as cytokines or adhesion molecules that might be involved in the fibrotic processes seen with scleroderma. However, the rationale for trying PA with this patient was
based on a novel disease pathogenesis hypothesis that focuses on a later stage of the disease process.

A 1979 research paper [11] titled “Endothelial Injury in Scleroderma” commented that "Many, if not all, of the manifestations of scleroderma can be explained on the basis of functional and structural vascular compromise after repeated vascular insults, subsequent healing of vascular walls with proliferative vascular response, and luminal narrowing". We hypothesize that the "repeated vascular insult" to the endothelium may entirely or mostly result from aggregated red blood cells being repeatedly forced through capillaries that are only able to normally pass only a very few red blood cells at a time, as shown in Figure 1 below.

![Figure 1](image)

The exact mechanism(s) of the endothelial damage is currently not known but likely include direct mechanical effects tending to re-model vessel walls and changes due to local ischemia caused by abnormal distribution of red cell aggregates in the microvascular circulation.

If this hypothesis is correct, regardless of the biological processes that lead to increased RBC aggregation, any treatment that is able to decrease the tendency for aggregation should prevent the initial endothelial trauma that, in turn, leads to later fibrotic processes that ultimately cause the systemic damage seen in SSc. If the disease process is already established, then minimizing or eliminating RBC aggregation should, at a minimum, slow the rate of disease progression and potentially lead to long-term improvement in organs that can partially or totally regenerate over time.

An important study [13] looked at microcirculatory and hemorheological parameters in 18 SSc patients before and after a series of four weekly PA treatments. Raynaud's symptoms either disappeared or were remarkably reduced in all patients after the series of PA treatments. RBC flow velocity increased significantly (p<.001) and RBC aggregation and plasma viscosity were significantly lower (p < .001). After 3 years, four patients were still free of Raynaud’s symptoms but in 14 patients Raynaud’s symptoms returned 6 to 9 months after the last PA treatment. RBC aggregation and plasma viscosity returned to pretreatment levels in about 9 months, although RBC flow velocity remained significantly enhanced for about 24 months. Several other studies have also shown improved changes in laboratory markers and clinical improvements in systemic Scleroderma patients after a series of PA treatments [14,15,16].

For our case study we not able to obtain pre and post treatment measures of whole blood viscosity and RBC aggregation. When this treatment protocol was initiated (1993), no test for either measure was commercially available. However, ESR has been shown to be significantly correlated with RBC aggregation [17]. Table 1 demonstrates the steady reduction of ESR levels following PA treatments which further supports the hypothesis that PA significantly reduced RBC aggregation in the patient.
Scleroderma disease pathogenesis remains a controversial area, especially with regard to the role of scleroderma-specific antibodies and scleroderma blood hyperviscosity. The fact that SSc patients appear to consistently benefit from PA treatments does not settle this question directly since PA both lowers RBC aggregation and temporarily reduces levels of circulating potential possible pathogenic blood factors such as autoantibodies. Future research is needed to determine the relative contribution of RBC disaggregation and the reduction of potential circulating pathogenic factors to the beneficial effects seen from long-term use of PA treatments.

The consistent therapeutic benefits seen with PA suggests that reduction or prevention of increased RBC aggregation in scleroderma patients may have the potential to control or reduce the development of scleroderma symptoms. This benefit may be achieved with pharmaceutical treatments or simpler methods of blood filtration/separation other than standard PA.

**Conclusion**

Small pilot studies have consistently shown systemic scleroderma patients benefiting from PA treatments. This the first instance of a patient with limited cutaneous systemic scleroderma receiving PA over 22 years as the sole systemic treatment. The long-term benefits shown in this case study suggest that additional clinical research on the suitability and applicability of PA for treating at least some forms of systemic scleroderma is justified.

**References**


5 Volkov S, Utset TO, Schmitz A, Ellman M, Cao D, Sweiss N. Whole Blood Viscosity (WBV) and Digital Ulcers in Scleroderma Patients. *Fellow's Abstract F56, 2006 ACR/AHRP Annual Scientific Meeting, Washington, DC.*


