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## Successful Long-Term (22 Year) Treatment of Limited Scleroderma Using Therapeutic Plasma Exchange: Is Blood Rheology the Key?

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## Abstract

While a number of studies have shown short-term beneficial effects of therapeutic plasma exchange (TPE) for treating systemic sclerosis (SSc), there have been no reports on the very long-term usage of TPE as the sole systemic treatment intervention. We report the case of a male patient, originally diagnosed with limited systemic sclerosis (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 gastro esophageal 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 TPE treatments and he remains in complete remission. While the typical explanation for the therapeutic benefits seen with TPE focuses on temporary reduction of circulating antibodies or other pathogenic factors, we propose instead an explanation based on abnormal blood rheology as a novel disease pathogenesis model for SSc.

## Keywords

Limited Sclerosis, CREST Syndrome, Plasma Exchange, Plasmapheresis, Blood Viscosity

## Introduction

Systemic scleroderma (SSc) is a family of rare autoimmune diseases that primarily affect middle age women. SSc is disabling, disfiguring, and steadily progressive, attacking internal organs through fibrotic processes in addition to its characteristic skin changes. 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 limited cutaneous systemic scleroderma (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. The patient complained that his fingers were slightly swollen in the mornings and that he was experiencing finger stiffness as well. Initial ANA testing was positive (1:1280); subsequent testing showed that the patient was positive for anticentromere antibodies (ACA). These positive ANA and antibody results, plus the presence of Raynaud's and other relevant clinical symptoms, lead to a formal diagnosis of early stage CREST syndrome (the old name for lcSSc).

Over the next three years, the patient's symptoms progressed rapidly. Erosive esophagitis was confirmed by upper endoscopy in May 1991. By late 1993, the patient was on 40mg omeprazole BID with very poor control of gastro esophageal reflux disease (GERD) symptoms and complained of chronic severe chilling. Raynaud's symptoms were not well controlled with nifedipine 30mg BID. While minor nailbed capillary enlargement was visible upon physical exam, there was no evidence of digital ulceration, skin changes, calcinosis or telangiectasias.

In November 1993, the patient began to receive regular therapeutic plasma exchange (TPE) treatments. The protocol used was one volume exchange of 5% albumin, administered one treatment per week for four weeks, followed by a two-month interval with no treatments. This pattern was then repeated for 16 treatments during the first year. The rationale for this treatment protocol is discussed below.

After one year of TPE treatments (16 treatments), the patient reported reduction in GERD and Raynaud's symptoms and reduced chronic chilling. At the end of the second year of treatments (32 treatments), GERD symptoms were completely controlled by 20mg omeprazole BID, Raynaud's symptoms improved to mild even in cold weather with nifedipine dosing reduced to 30mg QD, nailbed capillary enlargement resolved, and the patient had a normal upper endoscopy.

An initial pulmonary function test (PFT) performed on 7/7/94 (about 8 months after commencing TPE treatments) showed significantly reduced diffusing capacity for carbon monoxide (DLCO/VA) at 68% of predicted. FVC was 115% of predicted and FEV1/FVC ratio was 82%, suggesting the absence of restrictive lung disease. A repeat PFT performed on 5/31/95 showed that DLCO/VA, FVC, and FEV1/FVC were essentially unchanged (69% of predicted, 117% of predicted, and 84%). A third PFT performed on 8/27/97 indicated that DLCO/VA had improved to 76% of predicted. FVC and FEV1/FVC (81%) remained stable (119% of predicted, 81%). A final PFT performed on 1/16/2001 showed that DLCO/VA had

improved to 81% of predicted, which is in the normal range (only gas exchange was measured on this final PFT).

As a test to determine if continued TPE was necessary to sustain symptom improvements, TPE was suspended on 12/5/96 to observe the natural progression of the disease. Approximately six months later, the patient again complained of reflux symptoms. TPE treatments were resumed on the previous schedule beginning 6/19/97. At one year after resumption of treatments (16 treatments), all reflux symptoms again disappeared (the patient remained on 20mg omeprazole BID dosing during this time period).

In 1998 and again in 2002, the patient tried to reduce omeprazole dosing, but quickly started to develop reflux symptoms again and had to return to 20mg BID dosing to remain reflux-free. In 2009, the patient again tried to reduce omeprazole dosing, but this time proceeded very slowly over a three-month time period. In contrast to previous attempts to reduce dosing, this withdrawal method yielded positive findings: the patient was able to stop omeprazole completely and has remained free of any reflux symptoms since 2009 without using any acid-blocking medication. While speculative, we believe it likely that the patient would have been able to stop omeprazole completely as early as 1996 had we known then about the rebound problem from attempting to stop PPIs too quickly.

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 but before TPE treatments had commenced. The potential significance of this marked reduction in ESR over time is discussed below.

(Insert Table 1 About Here)

As of the date of this report, the patient continues on the original treatment protocol and has received more than 355 TPE treatments using normal peripheral venous access. The patient is currently in excellent physical condition 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. His only remaining SSc-related medication is nifedipine 30mg QD for the residual Raynaud's symptoms.

## Discussion

While the patient was given a formal diagnosis of CREST Syndrome in early 1991, under the new 2013 ACR/EULAR guidelines [1], the patient would not quite meet the formal point-chart based requirements for a diagnosis of SSc. These new guidelines require symptoms totaling at least 9 points for a formal diagnosis of SSc but the patient only exhibited symptoms totaling 8 points (2: abnormal nailbed capillaries, 3: Raynaud's, 3: positive ACA). However, given additional clinical symptoms such as GERD, finger swelling, and severe chronic chilling, it is likely that a patient exhibiting the same symptom profile now would receive a diagnosis of probable early lcSSc.

Many patients with ACA positive lcSSc live near-normal lifespans but typically with steadily increasing disabilities over the years such as chronic digital ulcerations, calcinosis, and gradually decreasing lung function. However, about 22% of ACA positive lcSSc patients

develop pulmonary artery hypertension (PAH), which is the most serious complication in this variant of SSc, leading to significantly decreased survival [2]. On 7/7/94, our patient had a DLCO/VA of 68% of predicted. Since a DLCO/VA of less than 70% of predicted is a significant ( $p=.014$ ) predictor of future development of PAH [3], this suggests that untreated, our patient was at increased risk of developing PAH in the future.

There appear to be no reports in the literature of documented spontaneous reversal of symptoms such as GERD or increasing lung function. Note that our patient achieved almost complete reversal of symptoms after two years of regular TPE treatments with this improved state maintained for more than 20 years with continued regular TPE treatments. This finding supports the interpretation that the TPE treatments are responsible for these improvements. Even though we did not obtain a baseline pre-treatment measure of DLCO/VA before commencing TPE treatments, the steady improvement of this parameter over the following two years, as well as the steady and significant reduction in ESR following introduction of regular TPE treatments, are also consistent with the interpretation that these improvements were likely a direct result of the TPE treatments.

There are at least 39 reports in the literature documenting the use of TPE for treating patients with SSc [4], ranging from case reports to large scale studies [e.g., 5,6,7,8,9,10]. The usual rationale and the post hoc explanation for the benefits seen is the decreased level of some circulating factor(s) (e.g., autoantibodies or immune complexes, cytokines or adhesion molecules) involved in disease pathogenesis and the fibrotic processes seen in SSc. However, the rationale for trying TPE with the present patient was based on a novel pathogenesis hypothesis that focuses on a later stage of the disease.

Research studies [11,12,13,14,15] have consistently shown elevated blood viscosity in the majority of systemic scleroderma patients. The specific factor contributing to hyperviscosity, when reported, is increased red blood cell (RBC) aggregation. 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 [14].

A 1979 paper [16] indicated 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 mostly or entirely result from enhanced RBC aggregates affecting the microcirculation. The exact mechanisms of endothelial damage from aggregated RBC are currently unknown, but likely include direct mechanical effects tending to re-model vessel walls and changes due to local ischemia caused by abnormal distribution of red cells in the microcirculation [17].

Jacobs, et al. [18] evaluated 18 SSc patients before and after a series of four weekly TPE treatments. Raynaud's symptoms either disappeared or were markedly reduced in all patients, RBC microcirculatory flow velocity increased ( $p<.001$ ) and RBC aggregation was lower ( $p < 0.001$ ). After 3 years, four patients were still symptom free but in the others, Raynaud's symptoms returned within 6 to 9 months after the last TPE. 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 improvements in laboratory markers and clinical symptoms in SSc patients after a series of TPE treatments [19,9,20].

The four-week TPE schedule utilized by Jacob, et al. [18] was chosen based on studies that showed normalization of RBC aggregation after four weekly treatments [14]. They also found that hemorheological parameters returned to pre-treatment levels between 3 and 9 months following the end of the four-week treatment cycle, depending on the patient. The two-month intra-treatment interval was chosen to maximize the likelihood that normalized blood rheology would be maintained as long as possible.

For our case study, we were not able to obtain direct pre and post TPE measures of blood viscosity and RBC aggregation. However, erythrocyte sedimentation rate (ESR) has been shown to be significantly correlated with RBC aggregation [21] and we demonstrated (see Table 1) a steady reduction of ESR levels following TPE treatments, lending further support to the hypothesis that TPE significantly reduced RBC aggregation. It is interesting to note that the last three ESR measurements, done in 2003, 2006, and 2009 by the Westergren method were consistent at 4 mm/h. The earlier ESR measures done in 1991 (pre-treatment), 1994, and 1995 were done by the Wintrobe method. However, in the low range, ESR done by the Westergren method is about 30% less than ESR done by the Wintrobe method [22], indicating that the last three ESR measurements of 4 mm/h are consistent with the 1995 ESR of 6 mm/h done by the Wintrobe method. This suggests that maximum RBC disaggregation was achieved by no later than June 1995, after about 1 ½ years of regular TPE treatments.

Scleroderma disease pathogenesis remains a controversial area, especially with regard to the role of scleroderma-specific antibodies and blood hyperviscosity. The fact that SSc patients consistently benefit from TPE treatments does not resolve this controversy, since TPE both lowers RBC aggregation and temporarily reduces levels of circulating factors such as autoantibodies. Future research is needed to determine the relative contribution of reduced RBC aggregation and of circulating pathogenic factors to the beneficial effects of long-term TPE.

## Conclusion

This the first instance of a patient with limited cutaneous systemic scleroderma receiving TPE over 22 years as the sole systemic treatment. The long-term benefits in this case study suggest that additional clinical research is justified on the suitability and applicability of TPE for treating some forms of systemic scleroderma as well as on the role of blood rheology in systemic scleroderma disease pathogenesis and treatment.

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## Tables

Table 1

### Changes in Erythrocyte Sedimentation Rate

Date	ESR (mm/h)
11/20/91*	13‡
9/13/94†	10‡
6/23/95†	6‡
8/27/03†	4§
11/9/06†	4§
6/18/09†	4§

\* Pre-treatment

† Blood draw done before first TPE treatment of each 4-week treatment group

‡ ESR done by Wintrobe method

§ ESR done by Westergren method.