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Benefit of Long-Term Therapeutic Plasma Exchange Treatment in a Patient with CREST Syndrome (Limited Systemic Scleroderma): A 21-Year Success Story

John Weiss, MD PhD[1], Madhuchhanda Roy, MBBS PhD[1], Edward S Harris, MS[2]

Introduction

- Systemic Scleroderma (SSc) is a family of rare autoimmune diseases that mostly affects middle age women.
- The limited variant of systemic scleroderma is steadily progressive, attacking internal organs through fibrotic processes in addition to characteristic skin changes.
- Current treatment approaches focus on using immunosuppressants plus symptom specific interventions. Neither approach is currently very effective.

Pre-Treatment Case History

- Patient is a 68-year-old male, diagnosed in 1990 at age 43 with limited systemic scleroderma (then known as CREST Syndrome) following five years of increasing Raynaud's symptoms.
- Patient was ANA positive (titer 1:1280). Follow-on antibody testing showed positive anti-centromere antibodies.
- Over the next three years, symptoms progressed rapidly with steadily increasing gastro esophageal reflux disease (GERD) symptoms. Upper endoscopy showed erosive esophagitis).
- Pulmonary function testing performed in 1994 showed significantly reduced diffusing capacity of the lungs for carbon monoxide (DLCO/VA) at 68% of predicted.
- Patient complained of severe chronic chilling (required sweaters in summer).
- Cardiac arrhythmias (PACs) developed in 1995.
- Raynaud's and GERD symptoms poorly controlled by standard medications.

[1] University of Wisconsin School of Medicine, Department of Pathology and Laboratory Medicine, Madison WI.

[2] Scleroderma Education Project, Madison, WI. (Corresponding author: eharris@sclerodermainfo.org)

Treatment History

- Therapeutic plasma exchange (TPE) treatments were initiated in November 1993. Protocol used: 1 treatment per week for four weeks followed by a two-month interval with no treatments.

Patient Status After 1 Year of TPE Treatments (16 Treatments)

- GERD symptoms reduced, well controlled by 40mg omeprazole once per day.
- PFT showed DLCO low but stable at 69% of predicted.
- Raynaud's symptoms reduced but still present.
- Chronic chilling significantly reduced.

Patient Status After 2 Years of TPE Treatments (32 Treatments)

- GERD symptoms completely controlled by 20mg omeprazole once per day (normal upper endoscopy).
- Raynaud's symptoms still present but very mild.
- PFT showed that DLCO had improved to 76% of predicted.
- Chronic chilling completely gone.

Longer-Term Symptom Changes

- A PFT performed in January 1996 showed that DLCO had returned to normal.
- Cardiac arrhythmias resolved early in 1998.
- Erythrocyte Sedimentation Rate (ESR) changed markedly over time:

Date	ESR (mm/h)
11/20/91	13
Post-Treatment	
9/13/94	10
6/23/95	6
8/27/03	4
11/9/06	4
6/18/09	4

Current Status

- Patient is in excellent overall health; reports that he exercises at least two hours every day.
- Patient reports that his only current scleroderma-related symptom is persistent mild Raynaud's.
- All labs are within normal ranges.

Are Regular TPE Treatments Required Long Term?

- In December 1996, TPE treatments were stopped to observe the natural progression of the disease.

- Approximately 6 months later, GERD symptoms returned and regular TPE treatments were re-started. GERD completely resolved again after one year (16 treatments).
- A later attempt to increase inter-treatment intervals was suspended after GERD symptoms again returned when the inter-treatment interval was increased from 8 ½ weeks to 11 weeks.

Discussion

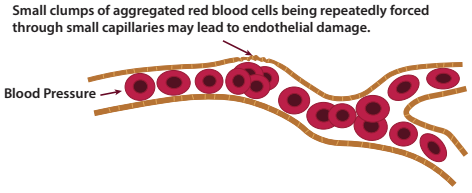
Why Does Therapeutic Plasma Exchange Work?

Reduction of Potential Circulating Pathogenic Factors

- TPE has been successfully tried with scleroderma patients since 1978, individually and in small pilot studies.
- The rationale for trying TPE has been based on the assumption that some circulating factor is involved in disease pathogenesis and plasmapheresis will temporarily reduce this potential circulating pathogenic agent.
- TPE temporarily reduces the levels of any potential circulating pathogenic factors. Each one volume exchange reduces 60% to 70% of circulating plasma components.[1]

Reduction of Blood Viscosity/RBC Aggregation

- A series of studies[2,3,4,5,6] published between 1975 and 2006 have consistently shown abnormally elevated blood viscosity in the majority of systemic scleroderma patients.
- The overall elevated blood viscosity is a direct result of abnormally aggregated red blood cells.[2,5]
- Early vascular damage is universally seen with systemic scleroderma. In 1979, Kahaleh et al. noted 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."[7]
- While speculative at this point, it is possible that aggregated red blood cells that are being forced by blood pressure though capillaries that are small enough so they normally permit passage of one red blood cell at a time may lead to the vascular damage cited above.



- In 1991, Jacobs et al.[8] documented that a single series of four weekly TPE treatments significantly reduced RBC aggregation and plasma viscosity ($p<.001$) for about 9 months and eliminated Raynaud's symptoms for 6 to 9 months in all subjects.

- ESR has been shown to be highly correlated with RBC aggregation.[9] While we have no direct pre- and post-treatment measures of blood viscosity/RBC aggregation, the observed reduction in ESR in our patient suggests the possibility that TPE may have contributed to a decrease in red blood cell aggregation.

Conclusion

- Small pilot studies have consistently shown systemic scleroderma patients benefiting from plasmapheresis treatments.
- This the first instance of a patient with limited systemic scleroderma receiving regular plasmapheresis treatments as the sole systemic intervention for a very long time period (21 years).
- The long-term benefits seen in this case study suggest that additional research on the suitability and applicability of long-term plasmapheresis for treating the subset of patients with limited systemic scleroderma is justified.

References

1. Derksen RH, Schuurman HJ, Meyling FH, Struyvenberg A, Kater L. The efficacy of plasma exchange in the removal of plasma components. *Journal of Laboratory and Clinical Medicine. 1984 Sep; 104(3): 346-54.*
2. Tietjen GW, Chien S, Leroy EC, Gavras I, Gavras H, Gump FE. Blood viscosity, plasma proteins, and Raynaud syndrome. *Arch Surg*. 1975; 110(11); 1343-6.
3. McGrath MA, Peek R, Penny R. Blood hyperviscosity with reduced skin blood flow in scleroderma. *Annals of the Rheumatic Diseases*. 1977; 36(6): 569–574.
4. Weber H, Schmid-Schonbein H, Lemmens H A J. Plasmapheresis as a Treatment of Raynaud's Attacks: Microrheological Differential Diagnosis and Evaluation of Efficacy. *Clinical Hemorheology* 1985; 5; 85-97.
5. Jacobs M J H M, Breslau P J, Slaaf D W, Reneman R S, Lemmens J A J. Nomenclature of Raynaud's phenomenon: A capillary microscopic and hemorheologic study. *Surgery* 1987; 101; 136-145.
6. 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.
7. Kahaleh MB, Sherer GK, LeRoy EC. Endothelial injury in scleroderma. *Journal of Experimental Medicine*. 1979; 149(6); 1326-1335.
8. Jacobs M J H M, Jorning P J G, von Rhede van der Kloot E J H, Kitslaaar P J E H M, Lemmens, H A J, Slaaf D W, Reneman R S. Plasmapheresis in Raynaud's phenomenon in systemic sclerosis: a microcirculatory study. *International Journal of Microcirculation: Clinical and Experimental* 1991; 10; 1-11.
9. Baskurt O, Björn N, Meiselman HJ. Red Blood Cell Aggregation. Boca Raton: CRC Press 2011.