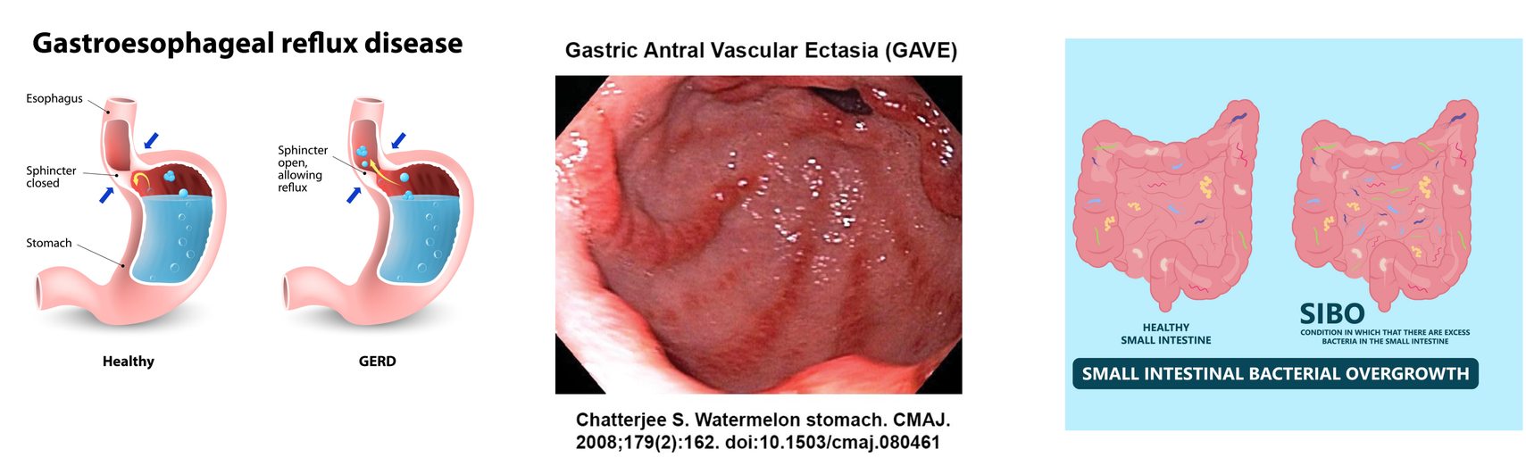
The Effects Of Pulsed Therapeutic Plasma Exchange On Gastrointestinal Symptoms In Limited Systemic Sclerosis: A Case Series

Edward S Harris MS[1], John W Weiss MD, PhD[2], Stephanie M Lacson, MD, FACR[3]

[1] Scleroderma Education Project, [2] University of Wisconsin, American Red Cross, [3] Kaiser Permanente West Los Angeles Medical Center

Background

- Systemic Sclerosis (SSc) is an umbrella term for a family of rare autoimmune diseases with the common factor being abnormal fibrosis of organ systems, including lungs, GI tract, kidneys, heart, and skin.
- Up to 90% of patients experience significant gastrointestinal (GI) symptoms such as gastro esophageal reflux disease (GERD), small intestinal bacterial overgrowth (SIBO), and Gastric Antral Vascular Ectasia (GAVE).
- No conventional treatment has been reported to reverse overall GI symptoms.
- Previous research on the use of the therapeutic plasma exchange (TPE) as a treatment for SSc has typically described clear improvements in clinical symptoms and laboratory markers with very few adverse events, but there has been almost no documentation of the effects on GI symptoms.
- This case series documents the effects on GI symptoms in four ANA positive patients diagnosed with anti-centromere antibody positive limited SSc, all of whom have been on the identical limited pulsed plasma exchange (PPE) protocol for time periods ranging from 18 months to 28 years.



Method

- Case series involving three or fewer patients are exempt from IRB approval at the University of Wisconsin, Madison. Patient one data is from a previously published case report. All patients included in this case series signed consent forms.
- Protocol: all patients receive a one blood volume TPE treatment per week for four weeks using sterilized 4% to 5% albumin as the plasma replacement. This is followed by an eight week no-treatment interval before the next cycle of four weekly treatments begins.
- Clinical assessment tools include the Scleroderma Health Assessment Questionnaire (SHAQ) and the UCLA Gastrointestinal Tract survey (GIT 2.0).

Results

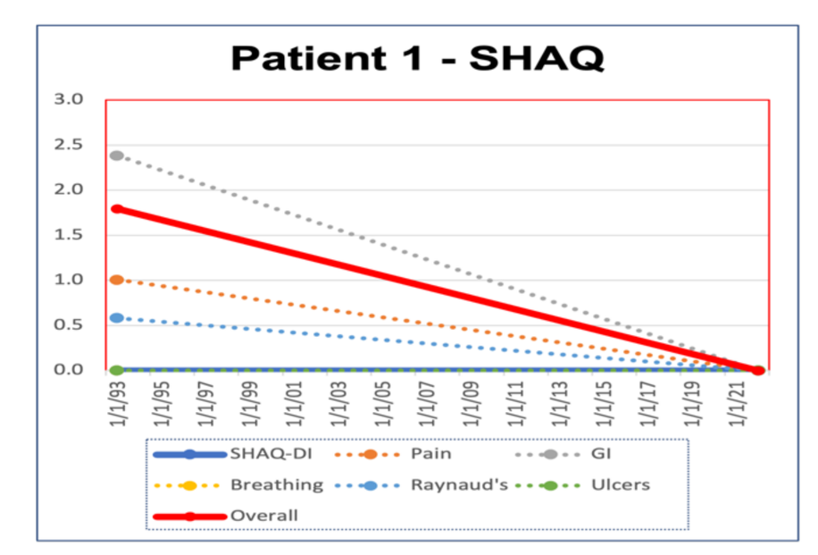
- No significant adverse events related to TPE treatments were reported in any patient.
- Each patient is summarized below.

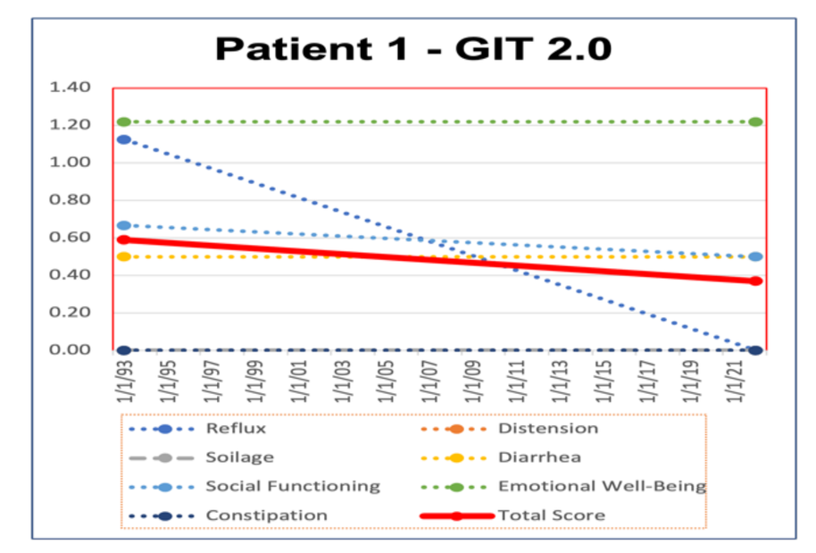
Patient One

- Male, diagnosed in January 1990 at age 43.
- Pre-PPE complaints included severe GERD, chronic cold intolerance, severe Raynaud's phenomenon (no digital ulcers), visible nailfold capillary enlargement, reduced DLCO/VA at 68%.
- Started PPE in November 1993; received approximately 490 treatments to date.
- After one year (16 TPE treatments), he reported significant reduction in GERD and Raynaud's and was able to reduce omeprazole dosing to 20mg BID (pre-PPE dosing was 40mg BID).
- At two years (32 TPE treatments), GERD was completely controlled with 20mg omeprazole QD, and he no longer reported cold intolerance. His DLCO/VA was stable at 68%. Over the next several years, his DLCO/VA score slowly increased and had returned to the normal range (82%) when last assessed in 2001.

Patient One (Cont.)

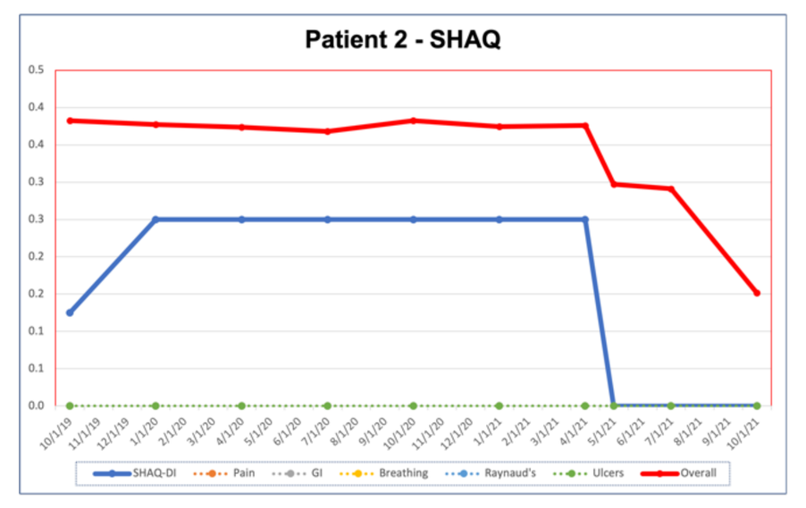
- The patient, currently aged 74, is in excellent overall health (he plays tennis almost every day). His only remaining SSc-related symptom is very mild Raynaud's. He was able to slowly taper completely off omeprazole in the late 90s and has no remaining GERD.

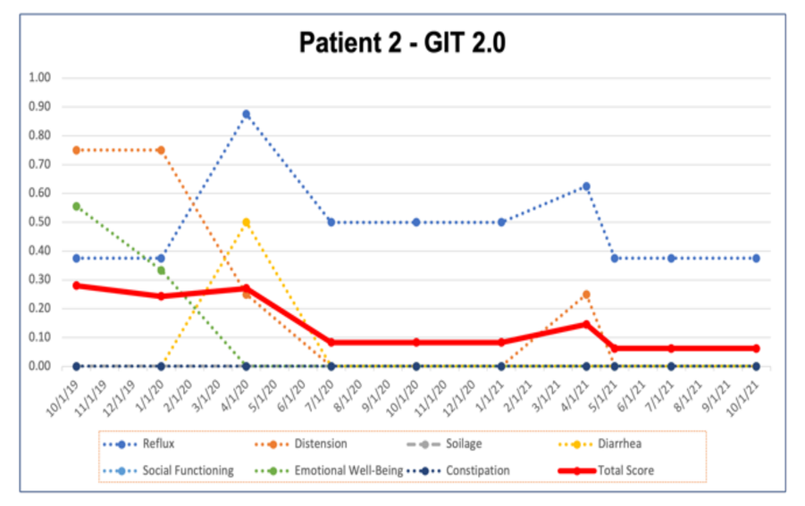




Patient Two

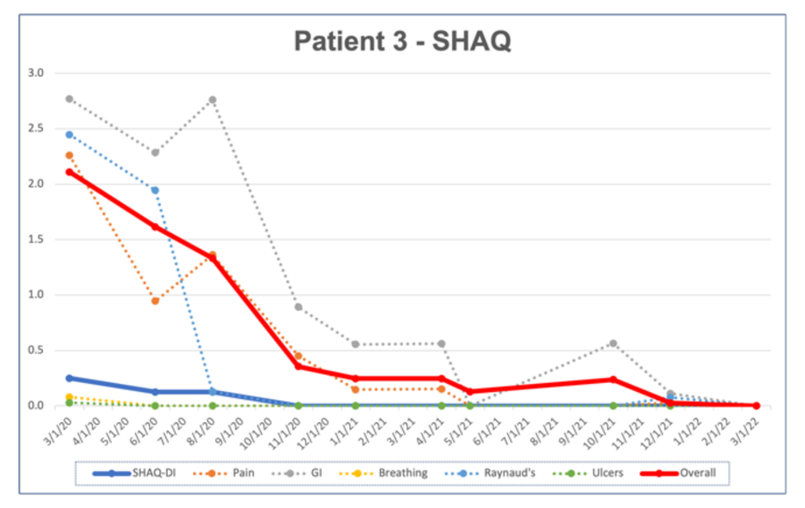
- Female, diagnosed with limited SSc in July 2019 at age 64.
- Pre-PPE complaints included GAVE, Reynaud's phenomenon, Sjogren's, GERD, telangiectasia, and visible nailfold capillary enlargement.
- She had six endoscopic laser surgeries between 2013 and 2019 as well as periodic iron infusions to control the bleeding / iron loss from GAVE.
- She started PPE in October 2019 and has received 38 treatments to date.
- Since starting PPE, she has maintained normal hemoglobin levels and has not required any further laser surgeries or iron infusions.
- She is currently 67, in very good health (participates in aerobics or weightlifting four days a week). She still suffers from Raynaud's, Sjogren's and GERD. She was diagnosed with a hiatal hernia about a year ago.

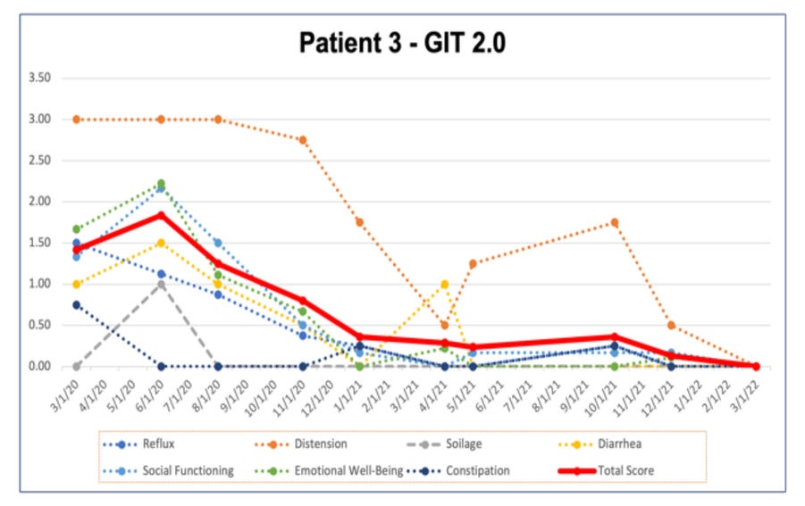




Patient Three

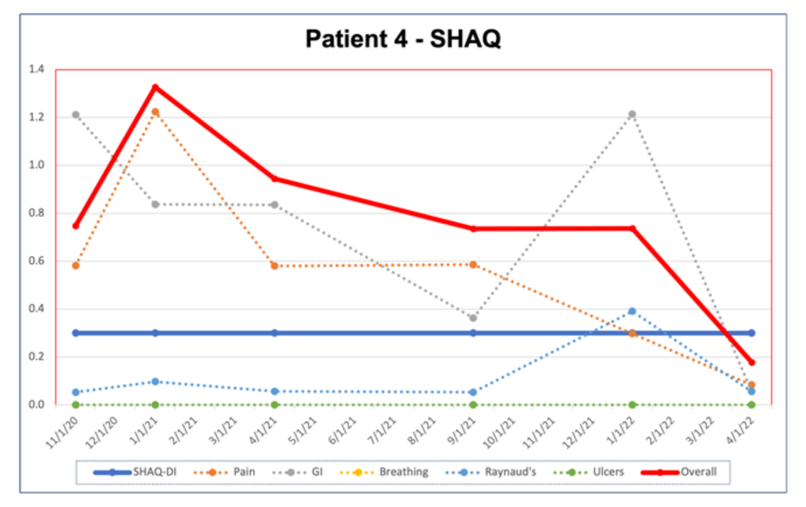
- Female, diagnosed with limited SSc in May 2017 at age 53.
- Pre-PPE complaints included gastroparesis, Raynaud's of hands and feet, cold intolerance, swollen fingers in mornings and evenings, calcinosis, chronic SIBO GERD, gastroparesis, esophageal spasms, constipation, fatigue, and myalgia. She was on 60mg dexlansoprazole QD for her GERD.
- She started PPE in March 2020 and has received 36 treatments to date.
- After 15 months of PPE, the esophageal spasms subsided, her GERD significantly improved, she no longer had to sleep on a wedge, and her fatigue had subsided.
- Her GERD, gastroparesis, and Raynaud's have greatly improved with continued PPE, and she has had no further calcinosis. She is slowly tapering off her reduced PPI dosing of 20mg esomeprazole QD.

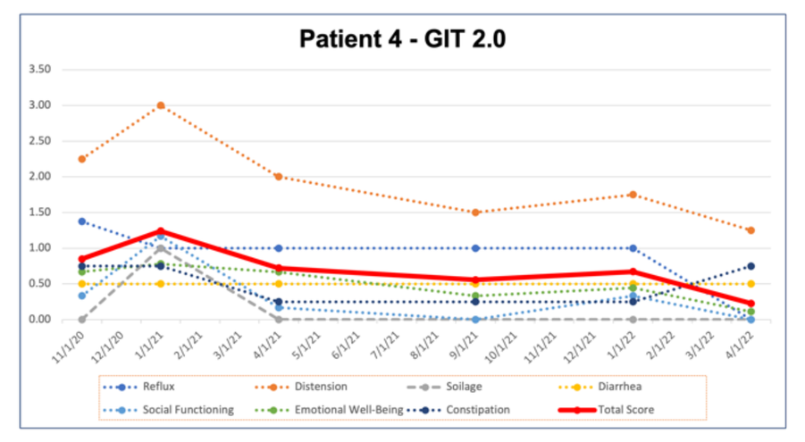




Patient Four

- Female, diagnosed with limited SSc in 1992 at age 34.
- Pre-PPE complaints included dysphagia, GERD, SIBO, and esophageal spasm, and increasing Raynaud's symptoms. She was unable to stand for long periods of time due to venous reflux and experienced difficulty sleeping at high altitudes.
- She started PPE in November 2020 and has received 24 treatments to date.
- After two treatment cycles, the patient reported reduced neck and shoulder pain and major improvement in esophageal spasms along with reduction of dysphagia. She reports further overall improvements with continued PPE.
- Her reduced venous reflux allows her to stand for longer periods of time and sleep at high altitudes is greatly improved.





Discussion

Current Treatments for GI Symptoms

- Treatment for GI involvement in SSc is almost entirely focused on symptom relief as conventional immunosuppressive treatments do not reduce the likelihood of developing severe GI symptoms.
- Typical treatments include PPIs for GERD, antibiotics for SIBO, and iron infusions/laser therapy for GAVE.

Systemic Interventions that Improve GI Symptoms

- **IVIg** – two small studies have documented improvements in GERD in patients while on IVIg.
- **HSCT (Autologous Hematopoietic Stem Cell Transplantation)** has also been shown to lead to improvements in GERD, GAVE, and dyspepsia that persisted for one to four years.
- Neither IVIg or HSCT can be used as a mainstream treatment for GI symptoms. IVIg cost is prohibitive for long-term use and HSCT caries significant risks and is used almost exclusively for high risk diffuse SSc patients

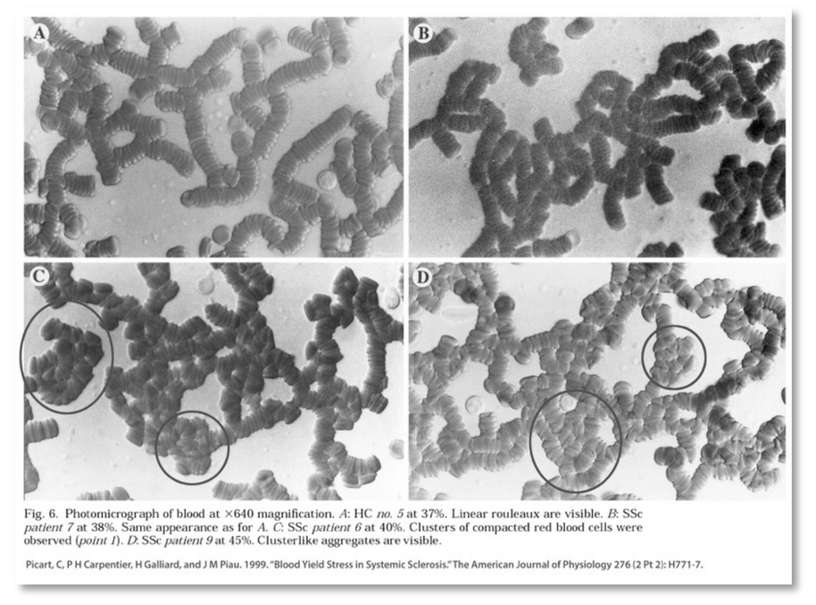
PPE – Possible Mechanisms of Action

- TPE is commonly used as an acute invention for diseases such as Guillain-Barré syndrome. The goal is rapid removal of pathogenic molecules such as auto-antibodies.
- In contrast, this PPE protocol has minimal effects on antibody levels because of the TPE administration frequency. IgG antibody levels are back to 70% of pre-TPE levels within three days of each TPE treatment.
- This suggests that the mechanism of action in this PPE protocol is unlikely to be from temporary reduction in antibody levels

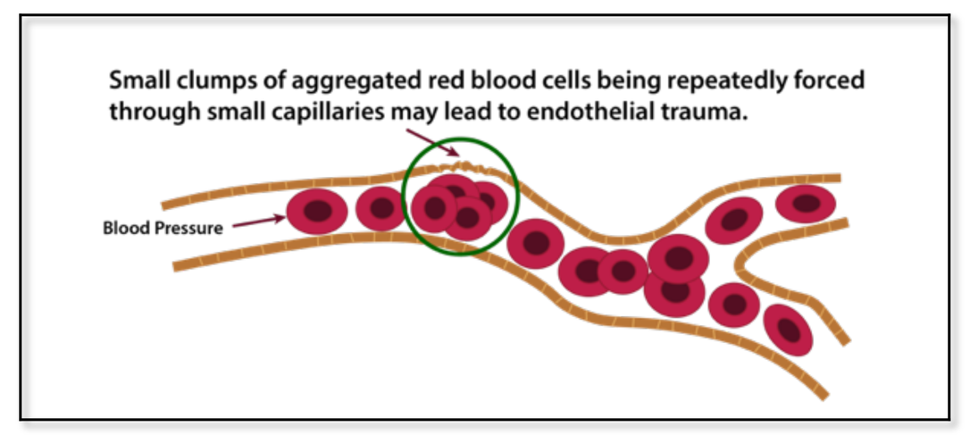
QR Code for an expanded handout with references

Abnormal Blood Rheology in SSc

- Over the past 42 years, many published papers have documented that blood rheology in patients with SSc is highly abnormal, including elevated whole blood viscosity (WBV), decreased RBC deformability, and abnormal RBC aggregation/clumping.
- 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."
- Two papers have documented the existence of tightly clumped RBCs in SSc patients. Here are images showing this phenomenon.



- One potential explanation for the early endothelial damage seen in SSc patients is from mechanical effects through local ischemia from clumped RBCs in the microcirculation:



- Previous research has demonstrated that a series of four weekly TPE treatments eliminates clumping of RBCs and normalizes overall blood rheology. These effects last for many weeks.
- The PPE protocol used in this case series is designed to keep blood rheology as close to normal as possible, potentially leading to a reduction in average endothelial trauma over time with the goal of reducing downstream fibrosis.

Long-Term TPE: Issues/Concerns

- Several studies have demonstrated that TPE has an excellent safety profile with minimal adverse events, almost always mild and transient specific to the procedure itself.
- This protocol recommends 5% albumin instead of fresh frozen plasma to minimize the risk of allergic reactions.
- Long-term TPE is significantly associated with the development of mild iron-deficiency anemia. This is easily treatable by over-the-counter iron supplements, but patient's serum iron levels should be monitored so supplement dosing can be monitored.
- Most patients can receive long-term TPE using normal peripheral IV access. In some patients, implantable ports may be a better option if venous access is challenging.

Conclusion

- GI involvement frequently has major impact on quality of life in patients with SSc.
- These preliminary results suggests that PPE should be considered in lcSSc patients with significant GI symptoms.
- Additional research is needed to better understand the mechanism of action in PPE and whether PPE is effective in SSc patients with different antibodies and clinical profiles.

References

See handout for reference list.

Contact: Ed Harris, CEO • Scleroderma Education Project • Website: SclerodermaInfo.org • Email: eharris@sclerodermainfo.org - Phone: 608-345-1984