Improvement of Severe Systemic Sclerosis-associated Gastric Antral Vascular Ectasia Following Immunosuppressive Treatment with Intravenous Cyclophosphamide

STEFFAN W. SCHULZ, MARIE O'BRIEN, MUHAMMAD MAQSOOD, NORA SANDORFI, FRANCESCO DEL GALDO, and SERGIO A. JIMENEZ

ABSTRACT. ***Objective.*** We describe 3 patients with systemic sclerosis (SSc) with severe, transfusion-dependent gastric antral vascular ectasia (GAVE) refractory to laser ablation who showed remarkable clinical and endoscopic improvement following intravenous (IV) pulse cyclophosphamide (CYC) treatment.
Methods. Review of clinical records and upper gastrointestinal endoscopy images from 3 patients with SSc and severe GAVE before and after treatment with IV pulse CYC.
Results. IV CYC was followed by improvement and stabilization of hemoglobin levels, and marked reduction in blood transfusion requirements and the number and frequency of endoscopic laser treatments.
Conclusion. IV pulse CYC immunosuppression was followed by remarkable clinical and endoscopic improvement of SSc-associated GAVE. (First Release July 15 2009; J Rheumatol 2009; 36:1653–6; doi:10.3899/jrheum.081247)

Key Indexing Terms:
SYSTEMIC SCLEROSIS GASTRIC ANTRAL VASCULAR ECTASIA
VASCULOPATHY IMMUNOSUPPRESSION CYCLOPHOSPHAMIDE

Systemic sclerosis (SSc) is an autoimmune disorder characterized by systemic fibrosis and severe vasculopathy affecting the skin and several organ systems including the lung, kidney, and gastrointestinal tract[1,2]. Gastric antral vascular ectasia (GAVE), a vascular gastric mucosal alteration characterized by capillary dilation, thickened and tortuous submucosal vessels, and fibromuscular hyperplasia[3-5], is often a severe and potentially life-threatening manifestation of SSc vasculopathy[6-9]. It was recently shown that intense immunosuppression improved some manifestations of SSc vasculopathy[10]. Further, resolution of GAVE was reported in a patient with SSc following cyclophosphamide (CYC) therapy[11]. We describe 3 cases of SSc with severe transfusion-dependent GAVE refractory to conventional therapy in whom there was remarkable clinical and endoscopic improvement following therapy with intravenous (IV) pulse cyclophosphamide (CYC). The results support the hypothesis that immunologic mechanisms are responsible for the development of this unique manifestation of SSc vasculopathy.

From the Jefferson Institute of Molecular Medicine, Division of Connective Tissue Disease, Department of Dermatology and Cutaneous Biology, Division of Rheumatology, Thomas Jefferson University, Philadelphia, Pennsylvania; and Division of Rheumatology, Lehigh Valley Hospital, Allentown, Pennsylvania, USA.

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S.W. Schulz, MD, Fellow, Division of Rheumatology, Thomas Jefferson University Hospital; M. O'Brien, DO, Division of Rheumatology, Lehigh Valley Hospital; M. Maqsood, MD, Division of Rheumatology, Thomas Jefferson University Hospital; N. Sandorfi, MD, Assistant Professor of Medicine, Division of Rheumatology, Thomas Jefferson University Hospital; F. Del Galdo, MD, PhD, Research Assistant Professor, Jefferson Institute of Molecular Medicine, Division of Connective Tissue Diseases, Thomas Jefferson University; S.A. Jimenez, MD, Professor, Co-Director, Jefferson Institute of Molecular Medicine, Director, Division of Connective Tissue Diseases, Thomas Jefferson University.

Address correspondence to Dr. S.A. Jimenez, Jefferson Institute of Molecular Medicine, 233 South 10th Street, Suite 509 BLSB, Philadelphia, PA 19107. E-mail: sergio.jimenez@jefferson.edu

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Case descriptions

Patient 1. A 59-year-old Caucasian woman developed Raynaud phenomenon, sicca symptoms, arthralgias, and rapidly progressive diffuse skin induration. She had a positive antinuclear antibody (ANA) test at a 1:1280 titer with both anticentromere and anti-Scl-70 antibodies. Severe anemia (hemoglobin 7.2 g/dl) requiring frequent blood transfusions prompted an esophagogastroduodenoscopy (EGD), which demonstrated the presence of GAVE with diffuse gastric vascular ectasias and distal antrum and duodenal bulb bleeding. She received a total of 13 YAG laser treatments with the last 6 applications administered at 4 to 6-week intervals between January 2006 and November 2006 to treat endoscopically visualized refractory sites of GAVE with persistent mucosal friability and bleeding. Twice-daily proton pump inhibitor therapy and oral iron supplementation

were added to her therapeutic regimen. Despite intensive interventional and pharmacological therapy during these months her anemia and the severity of visualized GAVE lesions on EGD were not substantially changed and she required 3 units of blood every 2–3 weeks. Owing to SSc lung involvement, she received IV CYC 750 mg/m^2 at monthly intervals starting from December 2006 through May 2007 and then every other month for an additional year. Five additional YAG laser treatments were given after starting CYC therapy between January 2007 and August 2007, and successive EGD performed at the same times showed serial improvement with fewer cumulative laser applications. Twelve months after initiation of CYC therapy (December 2007), blood transfusion requirements decreased to 3 units every 6 weeks, and after 18 months no further blood transfusions were necessary (Figure 1). Linear regression of the data shown in Figure 1 demonstrates high statistical significance with an r^2 value of 0.77 and $p < 0.0001$. Endoscopic evaluations at this time showed marked and sustained improvement of the gastric vascular ectasias requiring no further laser applications (Figure 2).

Patient 2. A 61-year-old Caucasian woman with a history of non-Hodgkin's lymphoma had bilateral hand and forearm skin induration, numerous telangiectasias, calcinosis, Raynaud phenomenon, and a positive ANA at titer 1:1280 with a nucleolar pattern, with SSc diagnosed in 1999. Three years after SSc diagnosis she developed pulmonary fibrosis and GAVE with severe chronic anemia (hemoglobin 6.0 g/dl) requiring frequent blood transfusions. EGD revealed severe mucosal friability with diffuse vascular ectasias of the gastroesophageal junction, cardia, antrum, and duodenum. She was treated with 16 YAG laser therapies between 2002 and 2005 with the concomitant use of Procrit, oral and monthly parenteral iron, twice-daily proton pump inhibitors, and ranitidine. The GAVE lesions were refractory, with continued fatigue, anemia (hemoglobin < 8 g/dl) requiring over 10 blood transfusions and persistent vascular ectasias, severe mucosal friability, and bleeding documented on numerous EGD. In May 2005 following the diagnosis of recurrent lymphoma, she received 6 monthly pulses of doxorubicin, oncovorin, rituximab, prednisone, and CYC. No YAG laser treatments were given during the chemotherapy. An EGD performed at the conclusion of chemotherapy in November 2005 revealed marked reduction in vascular ectasias in all regions of the stomach and duodenum without any active bleeding. Several subsequent EGD showed sustained resolution of GAVE lesions through the last evaluation 3 years after initiation of chemotherapy without the need for YAG laser applications. The endoscopic improvement was reflected by hemoglobin levels remaining above 10.0 g/dl without any blood transfusions.

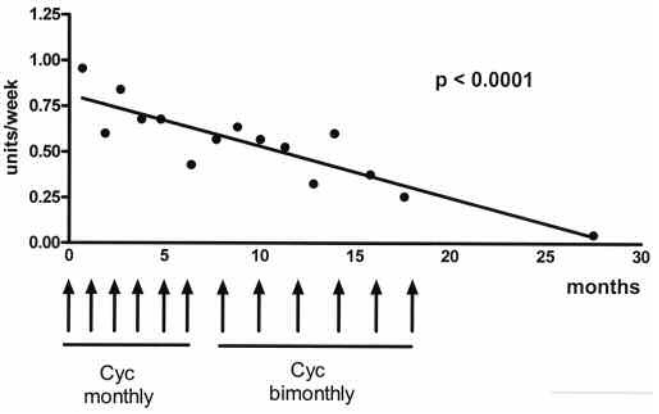

Figure 1. Units of blood required per week by Patient 1 over a 2-year period. Note significant reduction in transfusion dependence after initiation of intravenous (IV) pulse cyclophosphamide (CYC; 750 mg/m^2). Arrows show administration of IV pulse CYC. Following CYC treatment, no further transfusions were required. Linear regression analysis showed that the slope was highly significant with $p < 0.0001$.

Patient 3. A 45-year-old Caucasian woman had a history of diffuse SSc since 2000, with SSc renal crisis and bibasilar interstitial lung disease. She had a positive ANA (1:640 titer) in a speckled pattern. In 2002, she developed severe fatigue and anemia (hemoglobin 8.0–9.0 g/dl), and GAVE was discovered on EGD. The anemia and fatigue were refractory to 2 years of therapy with multiple YAG laser treatments and oral twice-daily proton pump inhibitors, and required biweekly infusions of iron and erythropoietin. Owing to rapidly progressive pulmonary involvement she was treated with monthly IV CYC (1000 mg/m^2) beginning in January 2004. No concurrent YAG laser therapies were administered during the CYC treatment. Within 8 months there was improvement in hemoglobin and iron levels (Figure 3), and no further erythropoietin or IV iron supplement was required. A linear regression analysis of the data in Figure 3 showed that the slope of serum hemoglobin levels before CYC therapy was not significant, whereas the slope following CYC was statistically significant ($p < 0.015$). Several EGD performed after the last CYC pulse in 2005 showed essentially complete and persistent resolution of the mucosal lesions.

DISCUSSION

The 3 patients with SSc described here had typical clinical manifestations and endoscopic evidence of GAVE, and all required blood transfusions, IV iron, ranitidine and proton pump inhibitors, and intensive YAG laser therapy for severe blood loss anemia; however, this therapeutic program failed to induce a sustained response. IV pulse CYC therapy was administered for treatment of SSc interstitial lung disease in 2 cases and recurrent lymphoma in one case. All 3 patients subsequently showed remarkable improvement of iron deficiency and associated anemia, reduction in blood transfusion dependence, and had endoscopically visualized, sustained eradication of esophageal, gastric, and duodenal vascular ectasias. The 3 patients had severe GAVE that was

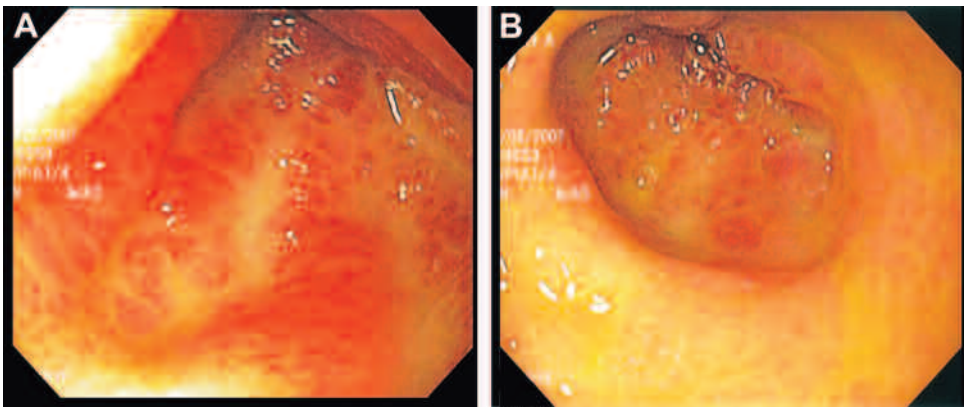

Figure 2. Endoscopic images of the antrum of Patient 1 at 2 months (A) and after 4 months of IV CYC (B). A. Dilated capillaries, tortuous and thickened vessels with mucosal friability and bleeding. B. Marked improvement in endoscopic appearance with essentially complete resolution of capillary dilation and mucosal friability after only 4 treatments of monthly IV CYC.

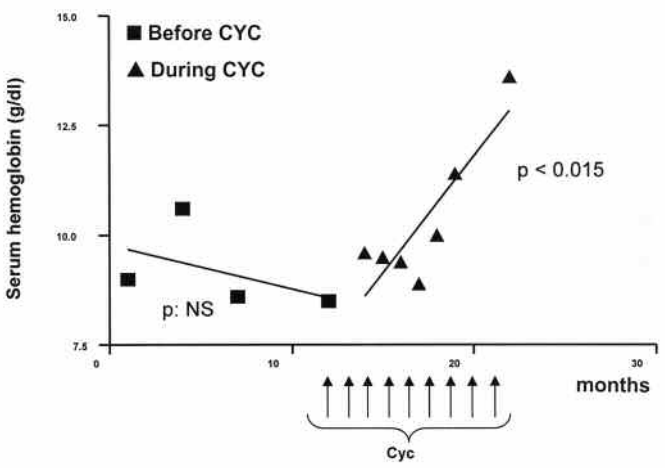

Figure 3. Serum hemoglobin levels of Patient 3 before and after IV pulse CYC. Data points are hemoglobin values with trendlines before and after initiation of 9 monthly CYC (1000 mg/m^2) infusions. Linear regression analysis showed that the slope prior to CYC therapy was not significant (NS), whereas the slope after start of CYC was significant.

refractory to currently accepted interventional therapies of neodymium yttrium-aluminum garnet (YAG) and argon plasma coagulation (APC) endoscopic laser treatments[12-15]. Their clinical course was similar to that of published cases in which there was recurrence of vascular ectasias despite intensive laser therapy[12,15-17]. Refractory cases of GAVE can be recognized by the return of bleeding, persistent hemoglobin level instability, and continuing transfusion dependence[12], and these cases mirror the presentation and clinical course of our patient cohort.

Increased understanding of the immunologic mechanisms responsible for SSc-associated vasculopathy has made immunosuppressive treatments such as IV CYC and bone marrow transplant novel therapeutic options. SSc vasculopathy and capillary abnormalities and rarefaction may result from inflammatory cell-induced dysregulation of endothelial cell functions[18]. Endothelial cell injury and capillary morphological changes and destruction resulting from this immunologic/inflammatory process are partially reversible with intense immunosuppression[10]. Indeed, SSc patients receiving high doses of immunosuppression and stem cell transplant displayed reversal of vascular disease, repopulation and regeneration of capillaries[19], and remarkable improvement of severe nailfold capillary abnormalities[10]. These reports strongly indicate that immunologic mechanisms initiate the small-vessel vasculopathy typical of SSc and perpetuate endothelial cell alterations. High-dose immunosuppression with CYC may "reset" the immune system by restoring a normal balance to the inflammatory cells and cytokines that ultimately cause vascular dysfunction. Since GAVE lesions very likely represent a manifestation of SSc vasculopathy, the 3 cases described here provide support to the hypothesis that other forms of SSc vasculopathy such as SSc renal crisis or SSc-associated pulmonary artery hypertension may also respond to intense immunosuppression. Although the observations described here are uncontrolled in the absence of a parallel group of SSc-GAVE patients not receiving immunosuppressive therapy, we believe that the remarkable temporal relationship showing almost immediate improvement of blood transfusion dependence, hemoglobin levels, and the severe endoscopic findings after initiation of CYC therapy are highly suggestive. Further controlled studies should evaluate the potential benefit of immunomodulating therapies for the treatment of GAVE and other severe and often fatal vascular complications of SSc.

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