Intravenous Cyclophosphamide for Gastric Antral Vascular Ectasia Associated with Systemic Sclerosis Refractory to Endoscopic Treatment: A Case Report and Review of the Pertinent Literature

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Abstract:
Gastric antral vascular ectasia (GAVE) is a rare cause of chronic gastric hemorrhaging and iron deficiency anemia and is characterized by a distinctive endoscopic appearance. The main treatment of GAVE is endoscopic; however, medication is necessary in refractory cases. We herein report a 69-year-old woman with systemic sclerosis (SSc) who developed recurrent severe anemia after endoscopic treatment of GAVE that was successfully managed using intravenous cyclophosphamide (IVCY). The recurrence of GAVE after discontinuation of IVCY was successfully managed using a combination of IVCY and endoscopic treatment, without blood transfusion. Long-term IVCY may be indicated for refractory GAVE associated with SSc.

Key words: Gastric antral vascular ectasia, systemic sclerosis, intravenous cyclophosphamide

Introduction
Gastric antral vascular ectasia (GAVE) is an uncommon but significant cause of upper gastrointestinal hemorrhaging and iron-deficiency anemia (1) and is characterized by the presence of erythematous or hemorrhagic ectatic vessels within the antrum that are distributed either in a striped (watermelon) or diffuse punctate pattern (2, 3-6). Although the etiology of GAVE is unknown, it is associated with various underlying conditions, including liver cirrhosis, portal hypertension, chronic renal failure, aortic stenosis, thyroid disease, and connective tissue disease. GAVE is the most frequently encountered connective tissue disease in patients with systemic sclerosis (SSc) (7, 8).

SSc is an autoimmune disease characterized by vascular injury and fibrosis of the skin and internal organs. A variety of pathologic gastrointestinal conditions can arise in patients with SSc. The prevalence of GAVE in SSc is reported to range from 1% to 22.3% (9-11). Telangiectasia is frequently seen in patients with SSc and is reported to be associated with GAVE, suggesting that GAVE could be considered a vascular manifestation of SSc. In addition, an association between GAVE and anti-RNA polymerase III antibodies was recently reported (10, 12, 13).

Endoscopic therapy is the mainstay of management for patients with GAVE (5). Argon plasma coagulation (APC) has a more favorable side effect profile than laser photocoagulation (5, 14-17) and so has been the treatment of choice for these patients. However, APC has the disadvantage of a high recurrence rate in the range of 30%-60% (5). Medical treatment has also been considered as a second-line treatment for GAVE that is resistant to APC (18). There are presently three reports (six cases) describing the efficacy of cyclophosphamide in SSc-associated GAVE (SSc-GAVE) in the literature (19-21).

We herein report a patient with SSc-GAVE who presented with recurrent severe anemia after multiple APC sessions and was treated with a combination of APC and intravenous cyclophosphamide therapy (IVCY).
A 69-year-old woman with limited cutaneous SSc was admitted to our hospital with severe anemia in February 2014. She had had sclerodactyly accompanied by Raynaud’s phenomenon since December 2013. A skin biopsy revealed the excessive accumulation of collagen in the dermis, which was consistent with SSc. Antinuclear antibodies were positive at a titer of 1:1,280 with a discrete speckled nuclear staining pattern (centromere pattern). Anti-topoisomerase I (Scl-70) and anti-RNA polymerase III antibodies were negative. A complete blood count revealed a red blood cell (RBC) count of 2.45×10^12/μL, hemoglobin (Hb) of 7.5 g/dL, hematocrit of 26.1%, and white blood cell count of 4,300/μL. Coombs tests were negative. Serum vitamin B12, folic acid, thyroid hormone, and haptoglobin levels were all within normal range. Upper gastrointestinal endoscopy revealed multiple diffusely distributed red spots extending radially from the pylorus and involving the gastric antrum, consistent with GAVE (Fig. 1A). Colonoscopy revealed no specific findings. APC was performed for the treatment of the hemorrhagic vascular lesions (Fig. 2A*). Transfusion of two units of packed RBCs was required; her Hb levels continued to increase and were normalized after six APC sessions.

After cessation of APC, the Hb level started to decrease. She was hospitalized for recurrence of GAVE in February 2015, at which time her Hb was 8.6 g/dL with normal values of mean corpuscular volume (MCV) (99 fL) and serum iron concentration (76 μg/dL). Three more APC sessions were performed, and her Hb levels increased to the normal range without the need for transfusion. Her Hb levels were maintained for approximately three months after the final APC session but decreased thereafter.

In April 2016, the patient was hospitalized because of severe anemia and found to have an Hb level of 4.5 g/dL (Fig. 2B*). The anemia improved temporarily after transfusion with 10 units of packed RBCs; Hb levels decreased despite APC. Therefore, we initiated IVCY at a monthly dose of 700 mg in combination with the APC sessions. The Hb levels steadily increased thereafter, even after the cessation of APC (Fig. 2C*). Upper gastrointestinal endoscopy revealed a significant reduction in the ectatic vessels around the pylorus (Fig. 1C).

Because GAVE was considered to be in remission, IVCY was discontinued after a total of six courses. However, the patient’s Hb level started to decrease again despite iron supplementation and had fallen to 6.3 g/dL with low levels of...
MCV (79 fL) and serum iron concentration (14 μg/dL) by August 2017. The ability of IVCY to suppress GAVE was considered to not be long-lasting in this patient, so IVCY was restarted in combination with 1 session of APC therapy, which increased her Hb level to 11.3 g/dL, without the need for blood transfusion. Although her Hb level had decreased some months after APC with monthly IVCY therapy, it remained above 9 g/dL. Although upper gastrointestinal endoscopy revealed remnant ectatic vessels around the pylorus, the area of vasodilation was considerably reduced (Fig. 1E).

**Discussion**

Management of GAVE has typically included surgery (antrectomy), medication, and endoscopic treatment. The current treatment of choice for GAVE is endoscopic treatment (15, 16, 22). APC has been the most frequently used treatment for GAVE (4), but it has a high recurrence rate, especially in patients with SSc-GAVE (23, 24). The first and second courses of APC improved the anemia in our patient. However, APC failed to achieve sustained suppression of GAVE, so while the Hb levels did decrease, blood transfusion was still required, despite treatment with APC.

We therefore considered that medical treatment sufficiently able to suppress SSc-related vascular abnormalities was needed, and IVCY was initiated to treat the recurrent GAVE in this patient. IVCY increased the Hb levels both during and after the APC sessions in the periods when monthly IVCY was performed (Fig. 2E*). Although the Hb level decreased after the discontinuation of IVCY, a single session of APC was sufficient to maintain the level above 9 g/dL without blood transfusion after restarting IVCY (Fig. 2E*). Judging from the overall clinical course during treatment with IVCY, we consider that IVCY was beneficial for controlling the severe anemia due to SSc-GAVE in this patient.

Several mechanisms have been implicated in the pathogenesis of GAVE, including mechanical stress in the antral-pyloric region of the stomach, altered levels of vasodilating substances, autoimmunity, and hemodynamic changes, depending on the underlying clinical setting (25). The involvement of autoimmunity in SSc-GAVE is suggested by the association with anti-RNA polymerase III antibody. Furthermore, Manetti et al. demonstrated the presence of inflammation with prominent CD4+ T-cell infiltration and the increased expression of profibrotic cytokines in the gastric wall in patients with SSc, regardless of the presence of GAVE as a complication (26, 27). In addition, Bhatcharyya et al. recently described three patients with SSc-GAVE who were successfully treated with hematopoietic stem cell transplantation (HSCT) (28). Taken together, these observations suggest that humoral and cellular immune abnormalities may be involved in the pathogenesis of SSc-GAVE and that immunosuppressive agents may be an effective treatment modality.

In terms of medical treatments, corticosteroids, cyclophosphamide, thalidomide, tranexamic acid, interferon-alpha, calcitonin, cyproheptadine, and estrogen/progesterone have been used anecdotally in the treatment of GAVE (18). However, the number of relevant reports on medical treatments of SSc-GAVE is limited in the current literature (22). Corticosteroids have been used to treat GAVE (29), but there are no reports on the use of corticosteroids as a single agent (22). A case report described the use of estrogen and
progesterone in a patient with CREST syndrome complicated by primary biliary cirrhosis (30). There have also been three reports (involving six patients) on the use of IVCY for GAVE (Table) (19-21). Lorenzi et al. described a patient with diffuse SSC who presented with GAVE that was resistant to endoscopic treatments but completely resolved following one course of IVCY and intravenous methylprednisolone pulse therapy indicated for combination of APC and IVCY therapy. We believe that this report is a meaningful addition to the literature, given the pae of existing reports on the use of IVCY to treat SSC-GAVE. Further studies investigating the appropriate duration of IVCY therapy and subsequent maintenance therapy are now needed to improve management of SSC-GAVE.

The authors state that they have no Conflict of Interest (COI).
References


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