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【 CASE REPORT 】

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

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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 (2-6). 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).

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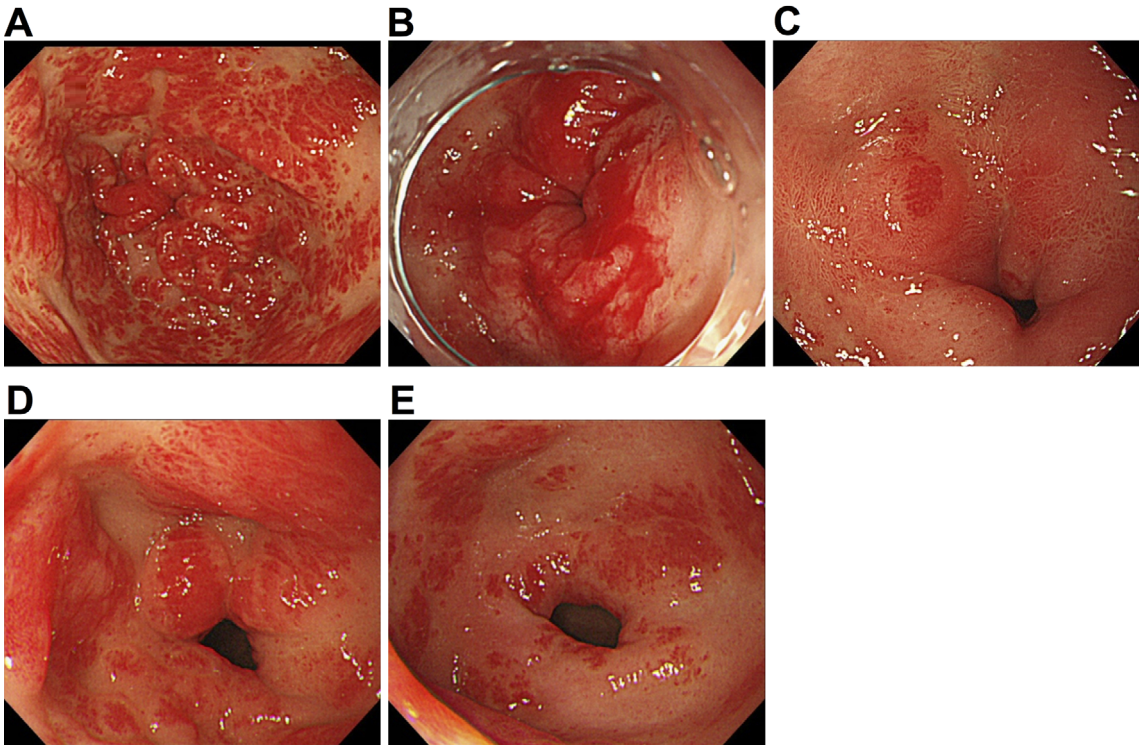

Figure 1. **Endoscopic images of gastric antral vascular ectasia (GAVE) in a patient with systemic sclerosis. A: Image taken during the first episode of GAVE with severe anemia requiring blood transfusion (February 2014) showing erythematous and hemorrhagic ectatic vessels radiating from the pylorus, distributed in a diffuse and punctate pattern within the antrum. B: Image showing recurrence of GAVE (April 2016). C: Image showing improved GAVE after four APC sessions in combination with six intravenous cyclophosphamide (IVCY) therapy sessions (October 2016). D: Image taken at the time of recurrence GAVE after discontinuing IVCY treatment (August 2017). E: Image showing reduced levels of ectatic vessels around the pylorus under IVCY treatment (February 2018).**

Case Report

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^{6}/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 B_{12}, 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. 2, A*). 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. 2, B*). 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. 2, C*). 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

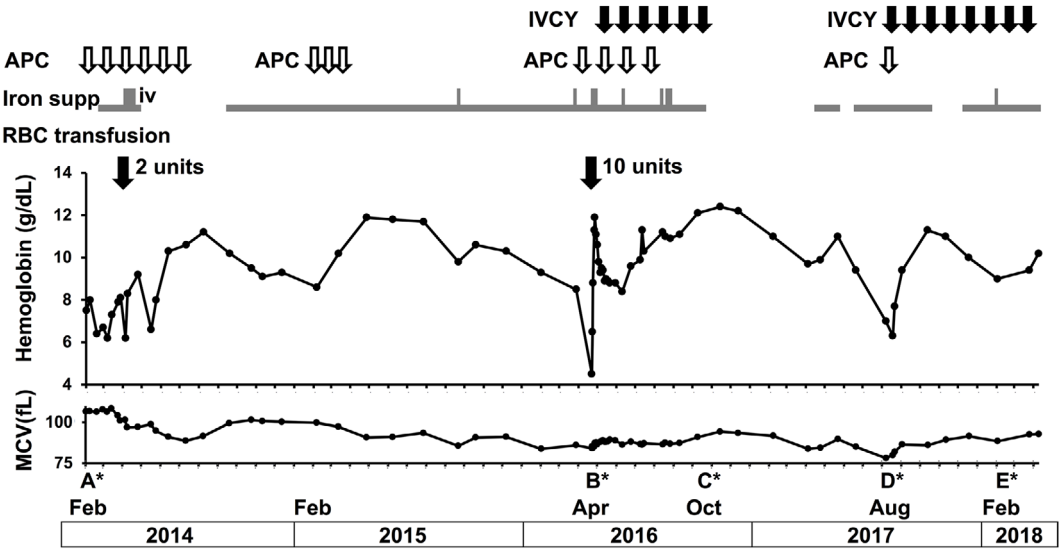

Figure 2. **Graph showing the hemoglobin and mean corpuscular volume (MCV) levels over time with the treatment history of gastric antral vascular ectasia (GAVE) associated with systemic sclerosis. *: A, B, C, D, and E represent the following time points: February 2014, April 2016, October 2016, August 2017, and February 2018, respectively, corresponding to A to E in Fig. 1. APC: argon plasma coagulation, IVCY: intravenous cyclophosphamide, RBCs: red blood cells, Iron supp: iron supplementation, iv: intravenous**

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. 2, C*). 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. 2, E*). 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 antropyloric 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, Bhattacharyya 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

Table. Clinical Features of the Present Case and Previously Reported Cases of Systemic Sclerosis Presenting with Intractable Gastric Antral Vascular Ectasia who were Successfully Treated with Intravenous Cyclophosphamide.

Patient	Age (years)	Sex	Type	Autoantibody	IVCY protocol	Ref
1*	69	F	Limited	ANA 1,280× (centrometric)	700 mg per month, 6 courses and 8 courses	
2	72	F	Diffuse	ANA 40×	10 mg/kg, 1 course**	[19]
3	45	F	Diffuse	ANA 320× (speckled)	750 mg/m^2 per month, 5 courses, followed by bimonthly administration for 1 year	[20]
4	61	F	Diffuse	ANA 1,280× (nucleolar)	Undescribed, 6 courses monthly***	[20]
5	59	F	Limited	ANA 1,280× (centrometric) Anti-Scl-70 Ab	1,000 mg/m^2 per month, 9 courses	[20]
6	69	F	Diffuse	ANA 1,280× Anti-RNAP III Ab	1,000 mg per month, 7 courses	[21]
7	50	F	Diffuse	ANA 640× Anti-RNAP III Ab	1,000 mg per month, 5 courses	[21]

*Our present patient. **Intravenous administration of methylprednisolone pulse therapy was used in combination with IVCY. ***Intravenous administration of cyclophosphamide. doxorubicin, vincristine, rituximab, and prednisone were used in combination for the treatment of non-Hodgkin's lymphoma. ANA: antinuclear antibody, ACA: anti-centromere antibody, Ab: antibody, anti-RNAP III Ab: anti-RNA polymerase III antibody, IVCY: intravenous cyclophosphamide, Ref: reference

progesterone in a patient with CREST syndrome complicated by primary biliary cirrhosis (30). There have also been three reports (involving six patients) on the efficacy of IVCY in SSc-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 concomitant interstitial lung disease (19). Schulz et al. described three patients with SSc-GAVE who showed no response to endoscopic treatment but showed clinical improvement with IVCY therapy (20). Papachristos et al. recently described two other patients with SSc-GAVE whose condition improved after IVCY therapy; one of these patients was the first reported case of IVCY administered specifically for the treatment of GAVE (21).

Of note, the patients with SSc-GAVE who were successfully treated with HSCT, as mentioned elsewhere, had received IVCY (2-3.75 g/m^2 in divided doses) prior to HSCT, which did not alter the course of GAVE, and all patients remained transfusion-dependent (28). Therefore, the response of SSc-GAVE to cyclophosphamide is considered to vary from patient to patient. We believe that our patient had an adequate response to IVCY, at least in the sense that IVCY enabled us to reduce the number of APC sessions needed to control GAVE without blood transfusion. The long-term administration of cyclophosphamide is associated with serious side effects, so a maintenance immunosuppressive regimen, which might include prolonging the interval between doses of IVCY or switching from IVCY to a less toxic agent, e.g., azathioprine or cyclosporine, will be needed in this patient.

As a limitation of this case report, from the perspective of endoscopic observation, the improvements in GAVE (Fig. 2, C* and E*) could not be conclusively attributed solely to IVCY therapy, as this therapy was used in combination with APC. It can also be argued that the intervals between GAVE relapses appeared to be similar before and after IVCY treatment and that blood transfusion was also unnecessary at the second APC session performed in February 2015, when the degree of anemia was less severe than in August 2017. However, the MCV and serum iron levels were lower in August 2017 than in February 2015. Therefore, if iron supplementation therapy had been appropriately increased by August 2017, it might have been possible to prevent her Hb level from dropping to such a low level. We also cannot exclude the possibility that the efficacy of IVCY in this patient might have been coincidental. The accumulation of more case reports describing the use of IVCY for patients with SSc-GAVE, especially the endoscopic evaluation of the efficacy of IVCY alone, is therefore warranted.

In conclusion, we encountered a woman with GAVE associated with anti-centromere antibody-positive limited cutaneous SSc who developed recurrent severe anemia after the cessation of APC and was managed successfully by a combination of APC and IVCY therapy. We believe that this report is a meaningful addition to the literature, given the paucity 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).

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