

Gastric Antral Vascular Ectasia and Its Clinical Correlates in Patients with Early Diffuse Systemic Sclerosis in the SCOT Trial

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ABSTRACT. Objective. To describe the prevalence and clinical correlates of endoscopic gastric antral vascular ectasia (GAVE; “watermelon stomach”) in early diffuse systemic sclerosis (SSc).

Methods. Subjects with early, diffuse SSc and evidence of specific internal organ involvement were considered for the Scleroderma: Cyclophosphamide Or Transplant (SCOT) trial. In the screening procedures, all patients underwent upper gastrointestinal endoscopy. Patients were then categorized into those with or without endoscopic evidence of GAVE. Demographic data, clinical disease characteristics, and autoantibody data were compared using Pearson chi-square or Student t tests.

Results. Twenty-three of 103 (22.3%) individuals were found to have GAVE on endoscopy. Although not statistically significant, anti-topoisomerase I (anti-Scl70) was detected less frequently among those with GAVE (18.8% vs 44.7%; $p = 0.071$). Similarly, anti-RNP antibodies (anti-U1 RNP) showed a trend to a negative association with GAVE (0 vs 18.4%; $p = 0.066$). There was no association between anti-RNA polymerase III and GAVE. Patients with GAVE had significantly more erythema or vascular ectasias in other parts of the stomach (26.1% vs 5.0%; $p = 0.003$).

Conclusion. Endoscopic GAVE was present on screening in almost one-fourth of these highly selected patients with early and severe diffuse SSc. While anti-Scl70 and anti-U1 RNP trended toward a negative association with GAVE, there was no correlation between anti-RNA Pol III and GAVE. Patients with GAVE had a higher frequency of other gastric vascular ectasias outside the antrum, suggesting that GAVE may represent part of the spectrum of the vasculopathy in SSc. (J Rheumatol First Release Feb 15 2013; doi:10.3899/jrheum.121087)

Key Indexing Terms:

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Gastric antral vascular ectasia (GAVE) is an endoscopic finding in which dilated submucosal vessels radiate in a spoke-like fashion from pylorus to antrum¹. The appearance of GAVE resembles the stripes of a watermelon, hence its pseudonym “watermelon stomach.” The clinical presentation ranges from asymptomatic anemia to severe bleeding. Although relatively rare, GAVE causes up to 4% of non-variceal upper gastrointestinal (GI) bleeding², and is increased in frequency among individuals with systemic sclerosis (SSc)³. Of note, a negative gastric biopsy does not exclude GAVE, as the lesions are focal and may be missed on biopsy⁴.

The association of GAVE and SSc was initially reported in 1989 and expanded in subsequent studies^{5,6,7,8,9,10}. These reports have described clinically apparent GAVE: that is, patients presenting with anemia or GI bleeding who were found to have GAVE on endoscopy. The prevalence of clinically evident GAVE has been reported as 5.7% in 1 cohort of 264 patients with limited and diffuse cutaneous SSc⁸. Studies have also suggested that anti-topoisomerase I (anti-Scl70) may be a negative predictor for GAVE^{8,9,10} and that anti-RNA polymerase III (anti-RNA Pol III) may be a positive predictor for GAVE^{9,10,11}. However, no published studies have identified a prevalence of or clinical correlates for endoscopic GAVE in SSc patients without significant anemia that was suspicious for GI blood loss.

The objectives of this study were 3-fold: (1) to report the prevalence of endoscopic GAVE in this selected population of early diffuse SSc; (2) to examine the clinical features associated with GAVE in this population; and (3) to characterize endoscopic findings of GAVE in these patients.

MATERIALS AND METHODS

Study population. The study population included patients with early diffuse SSc considered for the Scleroderma: Cyclophosphamide Or Transplant (SCOT) trial who were undergoing upper GI endoscopy. The SCOT study is a randomized National Institutes of Health (NIH) sponsored trial of 12 monthly infusions of cyclophosphamide versus myeloablative therapy followed by CD34 selected autologous hematopoietic cell transplantation (Website: www.sclerodermatrial.org). Details of this trial are available at ClinicalTrials.gov (NCT00114530).

All subjects had diffuse cutaneous involvement and disease duration < 5 years, calculated from the onset of the first non-Raynaud symptom. In summary, SSc-related pulmonary disease of moderate severity [percentage of predicted forced vital capacity (FVC) between 45% and 70%] or prior scleroderma renal crisis (as defined by the Ancona criteria¹² with recovery of renal function with serum creatinine < 2 and creatinine clearance > 40 ml/min) was required for inclusion for SCOT. Exclusion for randomization included active GAVE (as defined by evidence of recent GI bleeding) because of potential risk of GI hemorrhage in the thrombocytopenic period following high-dose immunosuppressive therapy.

Procedure for esophagogastroduodenoscopy (EGD). All patients who were considered eligible for SCOT and who signed the screening consent were required to have upper endoscopy. Patients underwent screening endoscopy performed by a gastroenterologist according to local institutional procedures and SCOT consents. Biopsies were performed if clinically warranted. The diagnosis of GAVE was confirmed by characteristic endoscopic findings of erythematous longitudinal stripes involving the

antrum and converging on the pylorus. Active GAVE was defined as evidence of recent or current bleeding. Erythema, ectasias, and esophagitis were defined per usual practice definitions. Delayed gastric emptying, which can be a sign of gastroparesis, was considered present if food was retained in the stomach after the overnight fast prior to the EGD.

Clinical variables. Baseline demographic data, disease characteristics, and clinical features were recorded at the time of screening including sex, age, ethnicity, body mass index (BMI), disease duration, and modified Rodnan Scleroderma Skin score (MRSS). Hemoglobin level, platelet count, creatinine clearance, percentage of predicted FVC, percentage of predicted DLCO adjusted for hemoglobin, and left ventricular ejection fraction on echocardiogram were documented. Right ventricular systolic pressure was included if provided in the echocardiogram report. Serum antibodies including anti-Scl70, anti-RNA Pol III, and anticentromere (ACA) were determined using commercial laboratories. Patients who did not have anti-RNA Pol III data available had this antibody determination made in the University of Texas-Houston Division of Rheumatology laboratory from stored repository sera.

These data were obtained in the prescreening phase of the SCOT trial to determine eligibility prior to randomization. Data from subjects who were not subsequently randomized in the trial were not subjected to data monitoring procedures of this trial and therefore are not included in the trial dataset. However, all data presented here were evaluated by authors (EWH, MDM, SA, VIM) and approved by all.

Statistical analysis. Pearson chi-square tests and Student t tests were used to compare demographics, disease characteristics, and clinical features among SSc patients with and without GAVE. Logistic regression analysis was used to correct for disease duration as a potential confounder.

RESULTS

Study population. A total of 103 patients underwent screening endoscopy for the SCOT trial. The majority of patients were female (74%) and 81.9% were white (Asian 9.6%, African American 4.8%, other 3.7%), with average age 46.5 ± 10.8 years and disease duration 1.7 ± 1.0 years. The mean MRSS was 29.6 ± 9.4 .

Although all subjects who were screened for the SCOT trial had upper endoscopy, not all subjects who were screened were subsequently randomized; autoantibody results, as well as stored sera, were available only for randomized subjects. Anti-Scl70 was detected in 37.0% of 54 patients, anti-RNA Pol III in 30.8% of 52 subjects, ACA in 8.2% of 49 subjects, and anti-RNP (anti-U1 RNP) in 12.9% of 54 patients.

Overall, 23 (22.3%) of 103 screened subjects had GAVE on endoscopy. Other endoscopic findings included esophagitis in 35.9%, dilated esophagus in 9.7%, other gastric vascular ectasias or erythema outside the antrum in 9.7%, food retained in the stomach indicating delayed gastric emptying or gastroparesis in 6.8%, and antral erosions in 4.9% of patients. There were no reported cases of Barrett’s esophagus or antral ulcers.

Demographic and clinical features. Comparisons of demographic and clinical features between patients with and without GAVE are given in Table 1. Patients with GAVE had a slightly higher BMI (27.4 vs 24.8; $p = 0.013$). There was also a slightly lower percentage predicted DLCO in the GAVE group (53.0% vs 58.9%; $p = 0.037$), which was

Table 1. Demographic and clinical characteristics of patients with and without gastric antral vascular ectasia (GAVE) during preliminary screening. Preliminary screening data were abstracted from patient charts. These data are not included in the SCOT clinical database and hence have not been subject to data management checks or onsite reviews by clinical monitors.

Characteristic	Patients without GAVE, n (%)	Patients with GAVE, n (%)	Group Comparison	
			OR (with:without) (95% CI)	p
Sex, female, %	72 (75.0)	22 (72.7)	0.89 (0.30, 2.62)	0.831
Race, white, %	69 (81.2)	22 (86.4)	1.47 (0.38, 5.72)	0.577
	n (mean)	n (mean)	Difference (without:with) (95% CI)	p
Age at enrollment, yrs*	80 (45.9)	23 (48.2)	-2.23 (-6.27, 1.81)	0.274
Disease duration, yrs	80 (1.6)	23 (1.9)	-0.32 (-0.81, 0.16)	0.189
Body mass index, kg/m ²	79 (24.8)	23 (27.4)	-2.69 (-4.79, -0.59)	0.013
Modified Rodnan skin score	78 (29.2)	23 (30.5)	-1.29 (-5.71, 3.13)	0.563
Right ventricular systolic pressure	49 (30.7)	12 (31.3)	-0.62 (-5.76, 4.52)	0.810
Left ventricular ejection fraction	78 (60.9)	21 (58.2)	2.69 (-0.59, 5.96)	0.106
FVC, % predicted	80 (75.6)	23 (78.4)	-2.75 (-9.96, 4.47)	0.452
DLCO, % predicted	66 (58.9)	19 (53.0)	5.83 (0.36, 11.29)	0.037
Hemoglobin level, g/dl	79 (12.4)	23 (11.8)	0.65 (-0.09, 1.38)	0.084
Mean corpuscular volume	80 (86.9)	23 (85.2)	1.77 (-1.14, 4.68)	0.231
Platelet count	80 (337.2)	23 (313.8)	23.3 (-32.74, 79.52)	0.410
Creatinine clearance, ml/min	75 (110.5)	22 (105.1)	5.43 (-14.91, 25.77)	0.598

* p values and CI use the Satterthwaite correction for unequal variances. FVC: forced vital capacity.

adjusted for hemoglobin. Otherwise there were no significant differences in the documented clinical features. Note that the p values in Table 1 are not corrected for multiple comparisons.

Autoantibody characteristics. Autoantibody data are shown in Table 2. Of the 103 patients with screening endoscopy, 54 were randomized to the SCOT trial and for whom autoantibody data were available. Overall, anti-Scl70 was found in 37% of these diffuse SSc cases. Anti-Scl70 was reported somewhat less frequently in patients with GAVE versus those without GAVE (OR 0.29, 95% CI 0.07–1.17, p = 0.071), although this difference did not reach statistical significance. Overall, anti-RNA Pol III was found in 31% of these diffuse subjects and we found no association between anti-RNA Pol III and GAVE (OR 1.36, 95% CI 0.37–5.00, p = 0.639). While anti-U1 RNP was found in almost 20% of

patients without GAVE, it was not present in any patient with GAVE (p = 0.066). After correcting for disease duration, we found similar results for association of autoantibodies with GAVE (data not shown).

Endoscopy findings. Endoscopic findings of patients with GAVE compared to those without GAVE are shown in Table 3. Patients with GAVE had significantly more vascular ectasias or erythema in other parts of the stomach such as the fundus or body (26.1% vs 5.0%; p = 0.003), whereas they had significantly less esophagitis (17.4% vs 41.3%; p = 0.036) than those without GAVE. There was no significant difference in the frequency of dilated esophagus or retained food in the stomach. Five patients without GAVE had antral erosions (6.3%), while in the GAVE group none did, although this difference did not reach statistical significance (p = 0.219).

Table 2. Comparison of autoantibody characteristics of randomized patients with and without gastric antral vascular ectasia (GAVE).

Autoantibody	Patients without GAVE, % Positive (no. positive/ no. tested)	Patients with GAVE, % Positive (no. positive/ no. tested)	Group Comparison	
			OR (with:without) (95% CI)	p
ANA	91.9 (34/37)	87.5 (14/16)	0.62 (0.09, 4.11)	0.616
Anti-Scl70	44.7 (17/38)	18.8 (3/16)	0.29 (0.07, 1.17)	0.071
Anticentromere	5.9 (2/34)	13.3 (2/15)	2.49 (0.31, 9.38)	0.380
Anti-U1 RNP*	18.4 (7/38)	— (0/16)	0.12 (0.01, 2.37)	0.066
Anti-RNA Pol III	28.9 (11/38)	35.7 (5/14)	1.36 (0.37, 5.00)	0.639

* Logit estimators with a correction of 0.5 in every cell are used for OR and 95% CI estimates. ANA: anti-nuclear antibody.

Table 3. Comparison of endoscopic findings of screened patients with and without gastric antral vascular ectasia (GAVE).

Endoscopic Finding	Patients without GAVE, n = 80 n (%)	Patients with GAVE, n = 23 n (%)	Group Comparison	
			OR (with:without) (95% CI)	p
Esophagitis	33 (41.3)	4 (17.4)	0.30 (0.09, 0.96)	0.036
Dilated esophagus	6 (7.5)	4 (17.4)	2.60 (0.67, 10.1)	0.158
Barrett's esophagus	0 (0)	0 (0)	NA	NA
Other gastric vascular ectasia or erythema	4 (5.0)	6 (26.1)	6.71 (1.70, 23.39)	0.003
Antral erosion	5 (6.3)	0 (0)	0.29 (0.02, 5.48)	0.219
Antral ulcer	0 (0)	0 (0)	NA	NA
Retained food	7 (8.8)	0 (0)	0.21 (0.01, 3.79)	0.142

NA: not available.

Results of *Helicobacter pylori* testing were available for 22 patients. Only 1 tested positive, and this patient did not have GAVE. Of the 23 patients with GAVE, 9 had had evidence of active or recent bleeding on endoscopy, and received endoscopic ablation with successful cessation of bleeding. Of these, 5 received argon plasma coagulation, 3 gold probe coagulation, and 1 received Halo 90 radio-frequency ablation.

Biopsy reports were available for 6 patients. Of these, 2 had biopsy reports specific for GAVE. One showed "stromal fibrosis and increased vascularity consistent with the clinical diagnosis of GAVE." One report simply stated "biopsies are consistent with watermelon stomach." The other 4 patients had nonspecific findings of chronic antral gastritis. As noted, a negative biopsy did not exclude the diagnosis of endoscopic GAVE.

DISCUSSION

The SCOT trial presented a unique opportunity to study the prevalence of GAVE in early and severe diffuse SSc, capitalizing on the screening procedures for enrollment in this trial. It is the first study to formally compare the clinical features and serologic findings in SSc patients with and without GAVE who were otherwise matched for disease duration and severity and were not preselected on the basis of anemia or GI symptoms.

Surprisingly, endoscopic GAVE was present in almost one-fourth of our patients with early and severe diffuse disease. This is higher than the previously reported 5.7% for clinically evident GAVE in 264 patients with limited and diffuse disease⁸. While this discrepancy might be explained by the difference in study population, which might lead to overestimation of the incidence of GAVE, our results demonstrate that endoscopic GAVE is common in this selected group of patients with early, severe diffuse SSc even in the absence of severe anemia. In fact, our subjects with endoscopic GAVE were not significantly more anemic than those without this finding. This implies that iron

deficiency anemia and GI bleeding may represent later stages of GAVE. The finding that esophagitis was less common in those with GAVE was a surprising result, which requires further study.

However, since complete concomitant medication histories on all subjects at the time of the EGD procedure were not available, it is possible that this difference could be explained by differences in the use of acid-suppressive therapy such as proton pump inhibitors or irritants such as nonsteroidal antiinflammatory drugs between these 2 groups of patients.

Confirming previous reports, our results indicate that anti-Scl70 antibodies may be negatively associated with GAVE. Ceribelli, *et al* reported no cases of GAVE among 101 anti-Scl70-positive patients with SSc¹⁰. In another report, anti-Scl70 was not detected in the serum of 6 diffuse SSc patients with GAVE, although half of 249 SSc patients without GAVE were anti-Scl70-positive⁸. In addition, Ingraham, *et al* found only 1 case of positive anti-Scl70 among 17 patients with diffuse SSc and GAVE⁹. We found anti-Scl70 present in almost half the patients without GAVE, but in only one-fifth of those with GAVE.

Previous reports postulated that anti-RNA Pol III may be associated with GAVE. This was first suggested in a case report by Yamamoto, *et al* of an SSc patient with GAVE and positive anti-RNA Pol III¹¹. Subsequently, Ingraham, *et al* identified a patient with GAVE in SSc who had positive anti-RNA Pol III⁹. After their study concluded, they found 4 additional diffuse SSc patients with positive anti-RNA Pol III in their clinical practice, and they found all had anemia on routine monitoring and GAVE on endoscopy. Ceribelli, *et al* conducted a retrospective chart review and identified 16 patients with positive anti-RNA Pol III, of whom 4 had GAVE¹⁰. Similarly, in our cohort, anti-RNA Pol III was detected in one-third of subjects with GAVE but also in almost 30% of those without GAVE, such that there was not much difference in the frequency of anti-RNA Pol III between those with and without GAVE. Overall, 31% of our

patient population had anti-RNA Pol III antibodies so this subset was fairly well represented. Prior reports were limited by lack of a comparison group^{9,11} or a comparison confined to patients with anti-Scl70 positivity¹⁰.

In a prior case series, only 1 of 28 patients with SSc and GAVE had anti-U1 RNP⁹. We similarly found that anti-U1 RNP trended toward a negative association with GAVE, being present in almost one-fifth of patients without GAVE, but absent in all with GAVE.

In our study, anti-RNA Pol III and anticentromere were not associated with GAVE, while anti-Scl70 and anti-U1 RNP trended toward a negative association with GAVE. Larger studies will be needed to address this further.

Different theories have been suggested to explain the pathophysiology of GAVE. One is that GAVE is largely mediated by vasodilation^{8,9,13}. Ingraham, *et al* found cutaneous telangiectasias in 61% of their SSc patients with GAVE⁹. Elevated gastrin levels have been reported in GAVE¹³, which could be explained by gastrin's vasodilatory effect. Further, there have been 4 cases of efficacy of cyclophosphamide in patients with refractory GAVE, suggesting that the vasculopathy of GAVE in SSc may be immune-mediated^{14,15}. On endoscopy we found GAVE was associated with significantly more vascular ectasias or erythema in other areas of the stomach beyond the antrum. Therefore, GAVE might represent part of the spectrum of immune-mediated vasculopathy in SSc, akin to telangiectasias and Raynaud phenomenon. In agreement with this hypothesis, we found GAVE was associated with a lower percentage of predicted DLCO, which may indicate pulmonary vascular involvement in SSc and further support the concept of GAVE as part of a systemic vasculopathy. Data regarding other clinical features, such as the extent and distribution of dermal telangiectasias as well as digital ulcers, were not recorded at screening because they did not affect eligibility, and therefore are not included in this analysis.

There are some potential limitations with our report. Our patient population was selected to include those with early diffuse SSc with either SSc-related pulmonary disease or a history of renal crisis, and thus may not be representative of all patients with diffuse SSc. Another limitation is that there was no standardized protocol for the EGD. Thus, early or more mild cases of GAVE could have been overlooked. Also, some of the observed significant associations regarding BMI and DLCO differences between patients with and those without GAVE may be a result of multiple comparisons. A statistical correction for multiple comparisons was not done because of the limited sample size of this unique patient group.

Overall, 37% had anti-Scl70 antibodies and 31% had anti-RNA Pol III antibodies. The number of subjects in the autoantibody subsets was relatively small, limiting our

ability to identify associations, as indicated by the wide CI in Table 2. Further studies are needed to investigate the clinical utility of early endoscopic screening in patients with diffuse SSc.

To our knowledge, this is the first study to examine the prevalence as well as clinical and serologic correlates of endoscopic GAVE in early diffuse SSc. Given the findings in almost one-fourth of screened subjects, we suggest that clinicians should have a lower threshold for endoscopic screening before initiating intensive cytotoxic therapy, which would result in severe thrombocytopenia in this select group of patients who are at risk for bleeding. While anti-Scl70 and anti-U1 RNP seemed to have a negative association with GAVE, there was no correlation between anti-RNA Pol III and GAVE. In addition, those with GAVE had more vascular ectasias or erythema in other parts of the stomach, suggesting GAVE may represent part of the spectrum of systemic vasculopathy in SSc.

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