Gastric Antral Vascular Ectasia in Systemic Sclerosis: Demographics and Disease Predictors

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Gastric Antral Vascular Ectasia in Systemic Sclerosis: Demographics and Disease Predictors

KRISTIN M. INGRAHAM, MARIE S. O'BRIEN, MAX SHENIN, CHRIS T. DERK, and VIRGINIA D. STEEN

ABSTRACT. ***Objectives.*** To evaluate patients with systemic sclerosis (SSc) who have gastric antral vascular ectasia (GAVE), to further characterize this disease association, and to identify factors that may predict which patients with SSc are at greatest risk for the development of GAVE.

Methods. Patients with a diagnosis of both SSc and GAVE were identified from the Division of Rheumatology at Georgetown University and Thomas Jefferson University. A chart review was conducted to obtain the demographic data.

Results. Twenty-eight patients were included in this analysis, including 17 with diffuse cutaneous (dcSSc) and 11 with limited cutaneous SSc (lcSSc). The mean disease duration at diagnosis with GAVE was 21.5 months for dcSSc and 84.3 months for lcSSc ($p = 0.025$). Seventy-six percent of patients with dcSSc developed GAVE within 18 months of first scleroderma symptom onset. Over half of patients with early GAVE also had rapidly progressive cutaneous disease. Only 4% had antitopoisomerase I antibody. Although only 1 patient was tested and had positive RNA polymerase (RNAP) III, RNAP III may be overrepresented in this GAVE population. Mean hematocrit levels were 23.8% in dcSSc and 29% in lcSSc.

Conclusion. dcSSc is associated with earlier development of GAVE, as well as more severe anemia requiring more therapeutic interventions. Rapid progression of cutaneous disease may suggest earlier development of GAVE. Absence of antitopoisomerase I antibodies and presence of antibodies to RNAP III/speckled antinuclear antibody pattern may be useful to identify the subset of patients with SSc with increased risk for GAVE. (First Release Jan 15 2010; J Rheumatol 2010;37:603–7; doi:10.3899/jrheum.090600)

Key Indexing Terms:
GASTRIC ANTRAL VASCULAR ECTASIA WATERMELON STOMACH SCLERODERMA SYSTEMIC SCLEROSIS

Gastric antral vascular ectasia (GAVE) is a rare cause of upper gastrointestinal (GI) blood loss that is often clinically silent until severe iron deficiency anemia is present and patients develop shortness of breath, excessive fatigue, and/or congestive heart failure. The distinctive endoscopic pattern is described as erythematous streaks on the longitudinal rugal folds traversing the antrum of the stomach and converging on the pylorus. As these streaks resemble the stripes on the outside rind of a watermelon, this condition is also known as "watermelon stomach." Histologic findings of GAVE include mucosal dilated capillaries containing pathognomonic fibrin thrombi, reactive foveolar epithelial changes, and fibromuscular hyperplasia of the lamina propria[1,2]. Both GAVE and portal hypertensive gastropathy (PHG) may be observed in patients with cirrhosis; however, PHG changes in the gastric mucosa are typically localized to the fundus or corpus and have a mosaic-like pattern[3]. Patients with GAVE often require multiple red blood cell transfusions and repeated endoscopic treatments with argon plasma coagulation[4].

Jabbari, *et al* formally defined GAVE and raised an association with autoimmune disease in 1984, although such a condition had been suspected in the 1960s[1,5] as a cause of anemia in patients with systemic sclerosis (SSc) and with cutaneous telangiectasias. In a series of 5 patients with GAVE and SSc, endoscopic biopsy specimens showed similarities between the vascular changes of GAVE and SSc, suggesting that watermelon stomach may represent a component of the spectrum of vascular alterations in SSc[6]. Larger series of patients with GAVE describe the association with SSc as well as with other autoimmune diseases such as pernicious anemia, hypothyroidism, and primary biliary cirrhosis[7,8]. To date there are only 2 small retrospective reviews of general characteristics of patients with watermelon stomach and SSc[6,9]. We evaluated our patients with both SSc and GAVE to further characterize this disease association and to identify factors that may predict which patients with SSc are at greatest risk for development of GAVE. Early-onset GAVE was defined as the diagnosis of GAVE

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within 18 months of the onset of the first SSc symptom. Rapidly progressive cutaneous disease was defined as the presence of diffuse involvement in upper extremities and trunk by 18 months from the onset of the first SSc symptoms.

MATERIALS AND METHODS

After receiving approval from the institutional review board of both institutions, patients with the diagnosis of both SSc and GAVE were identified from the Divisions of Rheumatology at Georgetown University and Thomas Jefferson University. In this case series only patients with endoscopic visual evidence of GAVE were included. A chart review was conducted to obtain the following data: patient demographics including race, sex, age, disease duration from first non-Raynaud's symptoms, SSc subtype, rate of disease progression, autoantibodies, prior medication use, SSc disease manifestations, other underlying medical conditions, and the outcome and treatment of GAVE. Autoantibodies were available through commercial laboratories. Any missing information was obtained by telephone interview with the referring physician and/or the patient. The Mann-Whitney U test was used to determine statistical significance between different patient subgroups.

RESULTS

Twenty-eight patients with SSc were identified who had been diagnosed with GAVE or watermelon stomach. The patients were predominantly women, with only 2 Caucasian males and 2 Hispanic females. Seventeen patients with diffuse cutaneous SSc (dcSSc) and 11 with limited cutaneous SSc (lcSSc) were identified (Table 1). Thirteen of the 17 (76%) with dcSSc had rapid progression of cutaneous disease, defined as the development of diffuse cutaneous disease involving extremities and trunk in the first 18 months from the first symptom of scleroderma.

Autoantibody profile results are presented in Table 2.

Table 1. General overview of demographic and associated antibodies for 28 subjects.

Characteristic		
Age (mean in yrs)	58 ± 10.9	
Female, %	93	
Race (Caucasian, Hispanic, African American), %	93, 7, 0	
dcSSc, no. (%)	17/28 (61)	
dcSSc with rapid progressive skin thickening, no. (%)	13/17 (76)	
Autoantibodies, %		
Antitopoisomerase	4	
Anticentromere	25	
Disease duration at diagnosis with GAVE (mean in months)		
Diffuse SSc	21.5 ± 26.6*	
Limited SSc	82.6 ± 84.3*	
Disease duration prior to GAVE, yrs	Diffuse SSc, %	Limited SSc, %
0–1.5	71	27
1.5–3	18	9
> 3	18	64

* p = 0.025. dcSSc: diffuse cutaneous systemic sclerosis; GAVE: gastric antral vascular ectasia.

Only 1 patient was antitopoisomerase I-positive (i.e., anti-Scl-70 antibody) compared to about 20% in the general population of patients with scleroderma at these centers. Two patients had the newer scleroderma-specific antibodies: 1 had positive RNA polymerase (RNAP) III antibodies and 1 was U3 ribonucleoprotein positive. In the 12 patients with dcSSc who did not have a defined scleroderma-specific antibody, 4 had a speckled antinuclear antibody (ANA) pattern and all 4 were in the rapidly progressive cutaneous disease group. Thus, it is likely that many of these patients in the rapidly progressive dcSSc group would have RNAP III antibodies because they had the typical clinical appearance and no anti-Scl-70, compared to 8% who had anti-Scl-70 antibody ($p < 0.05$, uncorrected). In the 11 patients with lcSSc, 7 (64%) had anticentromere antibody and another 5 had nucleolar pattern, while 4 had negative ANA.

The time from the onset of scleroderma symptoms to the diagnosis of GAVE varied greatly, from 2 months to 168 months (Table 3). Those patients in the dcSSc group were diagnosed with GAVE much earlier in the course of the disease (mean 21.5 mo, SD 26.6) compared to the lcSSc group (mean 82.6 mo, SD 84.3; $p = 0.025$). Sixteen patients were diagnosed with GAVE within 18 months of onset of symptoms, which we defined as early-onset GAVE. In this subgroup, 13 had dcSSc and 9 of these patients (69%) also had rapid progression of cutaneous disease. Two out of 3 patients with lcSSc and early-onset GAVE had anticentromere antibodies. Other vascular manifestations were commonly observed among all patients. Seventeen (61%) had cutaneous telangiectasias, 15 (54%) had a history of systemic hypertension, and 5 (18%) patients had digital ulcers. Four (14%) had scleroderma renal crisis, with 1 patient developing the condition before the diagnosis of GAVE was made. Six (21%) patients had pulmonary hypertension.

At the time of diagnosis of GAVE, 27 (96%) patients were found to have anemia. Many were asymptomatic and were diagnosed through routine laboratory studies. Nineteen of 28 (68%) patients were taking proton-pump inhibitors (PPI) at the time of GAVE diagnosis, including 9 of the 16 (56%) patients in the early-onset GAVE category. Eleven (39%) were taking nonsteroidal antiinflammatory drugs and 4 were taking corticosteroids. The dcSSc group also demonstrated a trend toward more severe GI blood loss. They had lower hematocrit levels and required more therapeutic interventions than the patients with lcSSc (Table 4), although these differences were not statistically significant. None of the patients was resistant to therapy.

DISCUSSION

This represents the largest series of patients with SSc and GAVE, an underrecognized vascular lesion of the stomach. It may be the primary cause of occult GI bleeding and severe anemia in SSc. Although a true prevalence of GAVE in SSc

Table 2. Ethnicity, scleroderma subset, and autoantibody findings in scleroderma patients with GAVE.

Patient	Sex	Ethnic Origin	SSc Subtype	Antibody
1	F	Caucasian	Diffuse*	Antitopoisomerase I
2	F	Caucasian	Limited	Centromere
3	F	Caucasian	Limited	Nucleolar
4	F	Caucasian	Diffuse*	U3-RNP
5	F	Hispanic	Diffuse*	Speckled
6	F	Caucasian	Limited	Centromere
7	F	Caucasian	Limited	Nucleolar and speckled
8	F	Caucasian	Diffuse*	Nucleolar
9	F	Caucasian	Limited	Centromere
10	M	Caucasian	Limited	Nucleolar
11	F	Caucasian	Diffuse	Antitopoisomerase I
12	F	Caucasian	Diffuse	Seronegative
13	F	Caucasian	Diffuse*	Speckled
14	F	Caucasian	Diffuse	Homogeneous
15	F	Caucasian	Diffuse*	Nucleolar
16	F	Caucasian	Limited	Centromere
17	M	Caucasian	Diffuse*	Seronegative
18	F	Caucasian	Diffuse*	Speckled
19	F	Caucasian	Diffuse*	U1-RNP
20	F	Caucasian	Limited	Centromere
21	F	Caucasian	Diffuse*	Seronegative
22	F	Caucasian	Limited	Centromere
23	F	Caucasian	Diffuse*	RNA polymerase III
24	F	Hispanic	Limited	Centromere
25	F	Caucasian	Diffuse*	Unknown ANA pattern
26	F	Caucasian	Diffuse	Seronegative
27	F	Caucasian	Diffuse*	Speckled
28	F	Caucasian	Limited	Speckled

* Rapidly progressive skin thickening. GAVE: gastric antral vascular ectasia; SSc: systemic scleroderma; RNP: ribonucleoprotein; ANA: antinuclear antibody.

Table 3. Comparison of general characteristics of patients with SSc and GAVE.

Characteristic	Watson, 1996, n = 5	Marie, 2008, n = 15	Our Series, 2009, n = 28
Female, %	100	80	93
SSc subsets, %	dcSSc, 60	dcSSc, 40	dcSSc, 61
Anticentromere antibody, %	40	66	25
Antitopoisomerase I antibody (anti-Scl-70), %	NA	0	4
Median time interval between SSc diagnosis and GAVE onset	< 36 mo*	36 mo (6-168)	10 mo (2-124)

* No exact time intervals reported. SSc: systemic sclerosis; GAVE: gastric antral vascular ectasia.

Table 4. Mean nadir hematocrit (HCT), transfusions, and laser treatments.

	Disease Pattern		
	Diffuse SSc	Limited SSc	p
Nadir HCT (%)	23.8	29	0.053
Blood transfusions, no.	5.5	2.2	0.285
Laser treatments, no.	3.6	2.7	0.147

is difficult to determine because of the relative rarity of SSc, one study estimated it at 5.7% in their population of 264 consecutive patients with SSc[9]. Table 3 provides a comparison of general characteristics between our population and patients with watermelon stomach described in 2 previous studies[6,9].

As in other studies, most of our patients were Caucasian females. There were no African American patients, although

about 20% of patients diagnosed and treated for SSc at each of our scleroderma centers are African American. Half of all our patients with scleroderma developed GAVE within 18 months of symptom onset. This was particularly true in the dcSSc group, in which 71% had very early disease (< 1.5 yrs). Although a few of the patients with lcSSc also had GAVE early in their disease, most of them had it after well established disease. The delayed development of GAVE in patients with lcSSc may represent the natural history of lcSSc as an illness with longstanding Raynaud's prior to the diagnosis of the disease. Table 3 shows that the time to GAVE diagnosis from symptom onset was somewhat shorter in our group than reported in the literature[6,9]. This discrepancy may have been either a result of earlier endoscopic screening for GAVE in our SSc subset with anemia, or simply a chance occurrence. In addition to early-onset disease in the patients with dcSSc, many also had rapid progression of skin thickening such that they had definite trunk involvement in the first year of the disease, suggesting that rapid skin progression may predict earlier GAVE development. In an abstract, 10.8% of patients with early severe dcSSc who were being screened for participation in the SCOT trial (Scleroderma, Cyclophosphamide, Outcome Study) had silent GAVE on required endoscopic evalution[10]. None of these patients was African American and they had a statistically significant higher forced vital capacity than patients without GAVE.

In terms of serologic evaluation, only 1 patient with dcSSc was tested and had positive RNAP III. However, it should be noted that 4 patients had speckled immunofluorescence pattern along with negative antitopoisomerase I antibodies, suggesting that they too could possess antibodies to RNAP III. A study has suggested that the ANA pattern that most commonly suggests anti-RNAP III antibodies was a fine speckled pattern with or without nucleolar staining[11]. Interestingly, just 1 of our patients had the antitopoisomerase I antibody, which is usually seen in about 15%–20% of patients with SSc, including up to 40% of patients with dcSSc[12,13]. A similar trend was observed by Marie, *et al*, who reported no patients with positive antitopoisomerase I antibody[9]. It is not clear whether this is a significant difference in the usual distribution of antibodies in scleroderma. However, with the high frequency of early dcSSc with rapid progression of skin thickening and the absence of the antitopoisomerase I antibody, it is possible that the RNAP III may serve as a predictor of GAVE development in this population. A report by Yamamoto, *et al* also described a case involving a patient with SSc with GAVE and RNAP III[14]. The presence of RNAP III is also strongly associated with renal crisis and less severe lung disease, and is less common in African Americans[15]. After completion of this study, 4 patients with RNAP III and dcSSc were found in our clinical practice to have new, asymptomatic anemia on routine monitoring and GAVE on endoscopic evaluation. All 4 required several laser treatments, but none required transfusions. Thus, because these tests are now commercially available, they should be obtained on all patients with SSc.

Prompt diagnosis of GAVE appears to be of significant clinical importance, as early intervention with iron or endoscopic laser treatment could prevent the significant morbidity associated with severe anemia. We noted previously that more than half our patients were taking PPI prior to diagnosis of GAVE. The role of PPI agents in treatment of GI manifestations of scleroderma has never been assessed in clinical trials; however, there might be at least a theoretical conflict between PPI use and GAVE. Formal association studies could not be performed because no comparison group was available. In one study, atrophic gastritis was present in all 19 biopsied patients from a group of 45 patients with watermelon stomach from any cause[7]. Prolonged PPI use has also been linked to development of atrophic gastritis and pernicious anemia[16]. It is possible that acid suppression from the use of these therapeutic agents may be contributing to atrophic gastritis and subsequently to GAVE, particularly in the susceptible patient. However, this seems unlikely in these patients with early dcSSc, and the increased use of PPI in our population may be related to the fact that all our patients were confirmed by endoscopy, most likely performed because of clinical symptoms such as gastroesophageal reflux disease, which was already being treated.

GAVE is a well defined disease that has been associated with scleroderma. It appears to have an increased prevalence in early dcSSc and in patients with late-onset anticentromere-positive lcSSc. Rapid skin worsening and possibly RNAP III antibodies may suggest earlier GAVE development. Further studies are required to test the utility of antibodies as disease markers in patients with SSc and GAVE, including antibodies against RNAP III. Absence of antitopoisomerase I antibody seems to be more common in patients with SSc and GAVE than in other patients with scleroderma. Anemia is uniformly present with GAVE and should be a strong clinical clue to early endoscopic evaluation for watermelon stomach. Careful monitoring and early diagnosis and intervention will make this an easier problem to manage.

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