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Gastric Antral Vascular Ectasia in Systemic Sclerosis: Association with Anti-RNA Polymerase III and Negative Anti-Nuclear Antibodies

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Abstract

Objective: Gastric Antral Vascular Ectasia (GAVE) is a vascular manifestation of systemic sclerosis (SSc) that can lead to iron deficiency anemia or acute gastrointestinal (GI) bleeding. We aimed to identify clinical features associated with GAVE.

Methods: We performed a cohort study of SSc patients who were seen at Stanford between 2004 and 2018 and had undergone esophagogastroduodenoscopy (EGD). We compared the clinical features of those with and without GAVE, and multivariable logistic regression was performed to identify clinical correlates with GAVE.

Results: A total of 225 patients with SSc who underwent EGD were included in this study and 19 (8.4%) had GAVE. Those with GAVE were more likely to have scleroderma renal crisis (SRC) (21% vs 3%; p<0.01), positive anti-RNA polymerase III antibody (71% vs 19%; p<0.01), nucleolar pattern of anti-nuclear antibody (ANA) (33% vs 11%; p=0.04), and negative ANA (<1:80 by immunofluorescence) (33% vs 11%; p=0.02). On multivariate analysis with multiple imputation, anti-RNA polymerase III positivity (OR 4.57; 95% CI (1.57 – 13.23), p<0.01) and ANA negativity (OR 3.75; 95% CI (1.21 – 11.62), p=0.02) remained significantly associated with GAVE.

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Conclusion: Positive anti-RNA polymerase III antibody and ANA negativity were significantly associated with GAVE. Further studies are necessary to determine whether patients with these autoantibody profiles should undergo screening endoscopies for GAVE.

1. Introduction

Gastric antral vascular ectasia (GAVE) is characterized by dilated small vessels, erythematous streaks, and longitudinal rugal folds in the antrum of the stomach. These findings are seen on esophagogastroduodenoscopy (EGD) and resemble the stripes of a watermelon, giving it the commonly known description of "watermelon stomach." EGD is the gold standard for diagnosis but is typically only performed when the clinical suspicion for GAVE is high. GAVE is more prevalent in patients with underlying cirrhosis, chronic renal failure, bone marrow transplantation, and autoimmune disorders.[1] Along with telangiectasias, pulmonary arterial hypertension, and scleroderma renal crisis, GAVE is one of the vascular manifestations of systemic sclerosis (SSc).

The prevalence of GAVE among SSc patients varies widely in different studies, with prevalence estimates ranging from 1–22.3%.[2,3] The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial enrolled SSc patients with early diffuse cutaneous disease as well as internal organ involvement, with either SSc-related pulmonary disease or history of scleroderma renal crisis, and found a high prevalence of GAVE in 22.3% of asymptomatic patients who underwent screening EGD prior to enrollment.[3]

GAVE can lead to iron deficiency anemia and acute gastrointestinal (GI) bleeding, and is therefore a potentially serious complication of SSc. Treatments include supportive interventions, such as blood transfusions, iron supplementation or infusions, and proton pump inhibitors, as well as procedural therapies such as endoscopic laser therapy and argon plasma coagulation.[4,5] There have also been reports of refractory cases being successfully treated with cyclophosphamide.[6,7] These modalities can be effective in both the treatment as well as prevention of GI bleeding, particularly if implemented early. Given that SSc patients with GAVE can be asymptomatic, and effective therapies exist to prevent GI bleeding which can be acute and severe, it is important to identify patients at risk of having GAVE who may benefit from screening endoscopy and treatments to prevent GI bleeding.

Prior studies have shown variable results in regard to autoantibody associations with GAVE, but the majority have suggested an association of anti-RNA polymerase III and GAVE. A study of the European Scleroderma Trials and Research (EUSTAR) cohort showed that anti-RNA polymerase III was associated with GAVE with an odds ratio (OR) of 4.6 (95% CI 1.2–21.1), and another study showed a prevalence of GAVE of 25% among patients with anti-RNA polymerase III, higher than the incidence in the general SSc population.[2,8] Another group described four patients with GAVE who had a positive ANA with a speckled pattern and a negative anti-Scl-70 but in whom anti-RNA polymerase III was not checked. They hypothesized that it was possible that these patients were positive for anti-RNA polymerase III and that there could be a correlation between GAVE and anti-RNA polymerase III though were not able to confirm this.[9] Although these studies support an association between anti-RNA polymerase III positivity and GAVE, further risk stratification

is necessary. In addition, the US SCOT trial did not find a significant association (OR 1.36; 95% CI (0.37–5.0)).[3] Instead, the SCOT trial showed a trend towards a negative association between GAVE and anti-Scl-70 and anti-U1-RNP antibodies.[3] Other studies have also suggested a low or nearly absent risk of GAVE among patients with anti-Scl-70.[8,10]

Other clinical associations with GAVE have also been reported; the EUSTAR study found an association between a low diffusing capacity for carbon monoxide (DLCO) (<75% predicted) and GAVE despite less frequent pulmonary fibrosis. Another study found that approximately 60% of SSc patients with GAVE have telangiectasias.[11] The aim of our study was to validate and identify novel associations with GAVE among our cohort of patients with SSc.

2. Materials and Methods

2.1: Study design and patient population

We performed a retrospective analysis of data on SSc patients enrolled into our clinical database at their first clinic visit at Stanford Hospital and Clinics from 2004–2018. All patients provided written informed consent prior to enrollment into the database. Data collected were confirmed by review of the electronic medical records. All patients fulfilled the 2013 ACR/EULAR classification criteria for SSc at the time of enrollment. Only patients who underwent EGD were included in the analysis. Patients were referred for EGD based on routine clinical indications such as gastroesophageal reflux (GER), dysphagia or esophageal dysmotility, anemia, GI bleeding, or other clinical concern. We performed a cohort study of SSc patients with and without GAVE as verified by EGD reports.

2.2: Data collection

Demographic data, clinical characteristics, and autoantibodies were collected. Clinical features were recorded as present if they had ever occurred in the patient's history, regardless of the timing in relation to the diagnosis of GAVE. A positive anti-nuclear antibody (ANA) was defined as an ANA with a titer of greater than or equal to 1:80 by immunofluorescence (IFA). Anti-centromere antibody positivity was defined as positive centromere antibody by enzyme linked immunosorbent assay (ELISA), or centromere pattern on ANA testing. Anti-Scl70, anti-U1-RNP, and anti-RNA polymerase III were detected by ELISA while anti-PM-Scl antibodies were detected by immunoblot or enzyme immunoassay.

2.3: Statistical analysis

Descriptive statistics were used to describe baseline characteristics and demographic data. Comparisons between GAVE and non-GAVE patients used Fisher's exact test for categorical variables, Student's t-test for age and Wilcoxon rank-sum test for all other continuous variables. For those variables with missing values, multiple imputation was performed by discriminant function for categorical variables and regression for continuous variables. Forty imputed datasets were generated and univariate analyses were performed, followed by multivariate analyses for the imputed datasets, and the pooled results were retained. History of scleroderma renal crisis was not included in the multivariate model because it is

significantly associated with anti-RNA polymerase III. All tests were two-sided and a p-value <0.05 was considered to be statistically significant. All analyses were done by statistical software with SAS, version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1: Demographics and Clinical Characteristics

We identified 323 patients who fulfilled ACR/EULAR classification criteria for SSc and 225 of these patients (69.7%) underwent EGD for any clinical indication. Among patients with GAVE, indications for EGD included anemia (37%), dysphagia or esophageal dysmotility (32%), GI bleeding (21%), and GER (10%). Indications for EGD in non-GAVE patients included GER (68.4%), dysphagia or esophageal dysmotility (16.5%), abdominal pain (4.9%), anemia (4.9%), GI bleeding (1.9%), malignancy screening (1.5%), hematemesis (0.5%), and pseudo-obstruction (0.5%); the indication for EGD was unknown in 1%. GAVE was diagnosed in 19 (8.4%) patients, and 206 had no evidence of GAVE on EGD. The mean age of the patients with GAVE at the time of GAVE diagnosis was 55.2 ± 13.8 years, and 89% were female. Among the patients who developed GAVE after their first non-Raynaud's symptom, the median time from the first non-Raynaud's symptom to diagnosis of GAVE was 3.1 years (range 0.1 to 16.5 years) after the first non-Raynaud's symptom. There was no significant difference in the time from the first non-Raynaud's symptom to detection of GAVE in the diffuse vs. limited subsets (median of 5.8 years (range 0.5 to 16.5) versus 3.4 years (range 0.1 to 11.2), respectively). Two patients were diagnosed with GAVE prior to the onset of any other non-Raynaud's symptoms attributable to SSc (two years prior and 14.5 years prior). Twelve (63%) of the 19 GAVE patients were treated with proton pump inhibitors, seven of whom received a proton pump inhibitor as the sole treatment for GAVE. Five (26%) of the patients required argon plasma coagulation, and two (11%) required other endoscopic cauterizations. The treatment was unknown for four (21%) of the patients. After a mean follow up time of 6.5 ± 2.9 years, 15 (79%) of the 19 GAVE patients were still alive. Four patients had died (at 1.4, 1.8, 2.2, and 4.5 years after the diagnosis of GAVE). The causes of death included respiratory failure due to interstitial lung disease and metapneumovirus; sepsis secondary to pneumonia; aspiration pneumonia; and metastatic non small cell lung cancer and pulmonary hypertension.

There was no significant difference in cutaneous subtype, disease duration from the first non-Raynaud's symptom to first clinic visit, or modified Rodnan skin score at the time of the first clinic visit between the patients with and without GAVE (Table 1). Patients with GAVE were significantly more likely to have had scleroderma renal crisis (21% vs 3%; p = 0.01). There were no significant differences in other clinical features including the presence of Raynaud's phenomenon, telangiectasias, interstitial lung disease, pulmonary hypertension, or cancer history between the two groups. Pulmonary function testing at the time of first clinic visit was also not significantly different between the groups. Hematocrit was not significantly different between the GAVE and non-GAVE groups at the time of the first clinic visit, but patients with GAVE had lower aldolase levels that trended towards significance (4.2 U/L vs 5.3 U/L; p=0.052).

3.2: Autoantibodies Associated with GAVE

GAVE patients were more likely than non-GAVE patients to have a positive anti-RNA polymerase III antibody (71% vs 19%; $p < 0.01$), a nucleolar ANA (33% vs 15%; p=0.04), and to have a negative ANA (33% vs 11%; p= 0.02) on univariate analyses (Table 2). Other autoantibodies such as anti-Scl-70, anti-centromere, anti-U1-RNP, and anti-PM-Scl did not demonstrate any statistically significant differences between the two groups. Table 3 illustrates the autoantibody patterns of each individual GAVE patient. Fifty percent of the anti-RNA polymerase III positive GAVE patients had a negative ANA. Additionally, all GAVE patients with a history of scleroderma renal crisis were positive for anti-RNA polymerase III. Lastly, the anti-RNA polymerase III status was unknown for the two patients who died with interstitial lung disease (patient 6 in Table 3) and pulmonary hypertension (patient 10 in Table 3).

3.3 Multivariable Logistic Regression Models

Univariate analyses identified anti-RNA polymerase III, negative ANA, a nucleolar ANA, and scleroderma renal crisis as strongly associated with GAVE, with a trend toward association with lower aldolase. These variables were included in the multivariable analysis except scleroderma renal crisis given the strong correlation with anti-RNA polymerase III. On multivariate analysis, anti-RNA polymerase III positivity (OR 10.98; 95% CI (2.97 – 40.63), $p<0.01$) remained significantly associated with GAVE, and ANA negativity (OR 3.30; 95% CI (0.97 – 11.23), p=0.06) was marginally significant in its association with GAVE (Table 4). Lower aldolase level was not significantly associated with GAVE. Given the number of missing anti-RNA polymerase III values, multivariable analysis with multiple imputation was performed. This revealed that anti-RNA polymerase III positivity (OR 4.57; 95% CI (1.57 – 13.23), $p<0.01$) and ANA negativity (OR 3.75; 95% CI (1.21 – 11.62), p=0.02) remained significantly associated with GAVE. We also performed a sensitivity analysis excluding 120 patients who were not tested for anti-RNA polymerase III antibodies. This showed similar results, with anti-RNA polymerase III (OR 10.11 (2.54 – 40.31); $p<0.01$) and ANA negativity (OR 5.65; 95% CI (1.35 – 23.66); p=0.02) still significantly associated with GAVE (Table 4). ANA negativity also remained associated with GAVE among patients with positive anti-RNA polymerase III (OR 18.75; 95% CI (1.68 – 209.54); p=0.02), but not in those who were negative for anti-RNA polymerase III (OR 1.70; 95% CI (0.16 – 17.86); p=0.66) (Table 4).

4. Discussion

Our study confirms findings from the EUSTAR cohort that found an increased odds of having GAVE in the presence of a positive anti-RNA polymerase III antibody. We also found a significant association between a negative ANA by IFA and GAVE, which has not been previously reported and may help with further risk stratification for GAVE among patients who are found to be positive for anti-RNA polymerase III. As RNA polymerase III is a nuclear antigen, patients with a positive anti-RNA polymerase III should theoretically also have a positive ANA. Among the GAVE patients, 5 out of 10 (50%) patients in our cohort who had a positive anti-RNA polymerase III positivity also had a negative ANA; in addition, amongst the anti-RNA polymerse III negative patients, ANA negativity was no

longer associated with GAVE. Thus, we considered whether the association of ANA negativity was driven by anti-RNA polymerase III positivity among the GAVE patients and whether these ANA values were falsely negative. Additionally, as there are other patients in our GAVE cohort who are ANA negative, anti-RNA polymerase III negative, and anti-Scl-70 negative, it is possible that some of these patients may have an unidentified autoantibody contributing to the risk of developing GAVE.

Unlike the SCOT study, we did not find an association between negative anti-Scl-70 or anti-U1-RNP antibodies and GAVE. However, our study population differed from that in the SCOT trial. Our cohort included a diverse population of SSc patients in a routine clinical practice, while the SCOT trial required patients to have early diffuse cutaneous disease as well as either SSc-related pulmonary disease or prior scleroderma renal crisis.

Our study has multiple strengths. Our patient population included both outpatient and inpatient encounters and therefore captured patients with a wide range of disease severity. All of our GAVE cases were confirmed by EGD based on clinical suspicion of disease, and we included only controls who had also undergone EGD to ensure that cases of GAVE were not missed. Finally, we had detailed clinical information and longitudinal follow-up on all GAVE patients.

Our study had some limitations, one of which was the relatively small number of GAVE patients in the cohort. While all patients included in our study underwent EGD, not all SSc patients in our clinical practice at our institution underwent EGD, and thus we were not able to estimate the true prevalence of GAVE within our overall population. There may be a selection bias in our cohort for patients with more active clinical disease given that they underwent EGD for evaluation of a clinical GI manifestation; thus, patients with occult GAVE or more mild disease may not be represented in our cohort. However, we were able to confirm a strong association between the anti-RNA polymerase III antibody and GAVE despite some missing data. Also of note, one of the GAVE patients died in part due to interstitial lung disease and one due to pulmonary hypertension; while the anti-RNA polymerase III status was not known for either of these patients, the patient who had interstitial lung disease had a positive nucleolar ANA and anti-Scl 70, both of which are associated with interstitial lung disease, and the patient who had pulmonary hypertension had a nucleolar ANA, which is associated with pulmonary hypertension.[12] There is data to suggest that anti-RNA polymerase III positivity is associated with a lower risk of interstitial lung disease[13] and pulmonary hypertension[14]. The anti-RNA polymerase III availability increased with time, and missing data for this parameter decreased over time, from 2004 through the more recent enrollment.

5. Conclusion

In conclusion, GAVE is a rare vascular manifestation in SSc patients and often identified in the setting of clinically significant GI bleeding or iron deficiency. Anti-RNA polymerase III positivity and ANA negativity were both independently associated with an increased risk of GAVE among SSc patients. Patients with a positive anti-RNA polymerase III should be monitored, particularly if they have a negative ANA, and if GI bleeding or iron deficiency

anemia develop, physicians should have a low threshold to perform EGD to evaluate for the presence of GAVE. Further studies are warranted to determine if these patients would benefit from screening endoscopy for the early detection and treatment of GAVE and additionally, to identify any other novel autoantibodies that may be associated with GAVE.

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Table 1:

Demographic and Clinical Features

	GAVE, n (%) (n=19)	Non-GAVE, n (%) (n=206)	p value
Age (years), mean (SD)	58 (13.2)	55 (13.2)	0.42
Female	17 (89)	183 (89)	0.93
White/Caucasian	14 (74)	133 (65)	0.86
African American	1 (5)	7 (3.4)	
Asian	2 (11)	26 (13)	
Pacific Islander	0 (0)	0 (0)	
Other or mixed	2 (11)	35 (17)	
Unknown	0 (0)	5 (2.4)	
SSc subtype (n=223)			0.06
Limited	9 (47)	129 (64)	
Diffuse	10 (53)	73 (36)	
Disease duration, years, median (range) * (n=209)	4.1 (0.5 – 33.7)	6.8 (0.4 – 60.3)	0.07
Glucocorticoid use (n=225)			0.28
Never	10 (53)	141 (68)	
Ever	9 (47)	65 (32)	
Digital ulcers (n=225)	6 (32)	67 (33)	0.93
Calcinosis (n=225)	6 (32)	44 (21)	0.38
Raynaud's phenomenon (n=225)	17 (89)	201 (98)	0.11
Scleroderma renal crisis (n=225)	4 (21)	6 (3)	<0.01
PAH (n=225)	4 (21)	35 (17)	0.75
ILD (n=225)	6 (32)	71 (34)	0.80
GER (n=225)	17 (89)	183 (89)	1.00
Cancer history (n=225)	2 (11)	20 (10)	1.00
Telangiectasias (n=225)	14 (74)	149 (72)	0.90
Modified Rodnan Skin Score, median (range) (n=211)	10 (0 – 39)	7 (0–41)	0.61
FVC, % predicted, median (range) (n=206)	94 (35 – 116)	90 (21 – 134)	0.64
DLCO, % predicted, median (range) (n=203)	72 (17 – 124)	75 (14–130)	0.58
RVSP on TTE, median (range) (n=210)	31 (19 – 83)	28 (14 – 81)	0.45
Creatine kinase (U/L), median (range) (n=218)	83 (4.9 – 379)	83 (20 – 1334)	0.86
Aldolase (U/L), median (range) (n=200)	4.2 (2.3 – 11.3)	5.3 (2.5 – 35.3)	0.052
Hematocrit (%), median (range) (n=202)	36.7 (28.7 – 43.7)	38.2 (26.3 – 53.7)	0.21

Terms: SD: standard deviation; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; GER: gastroesophageal reflux; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; RVSP: right ventricular systolic pressure; TTE: transthoracic echocardiogram

* Disease duration: time from first non-Raynaud's symptom to the time of enrollment into the study database

Table 2:

Autoantibodies

Positive Autoantibody	GAVE, n (%) (n=19)*	Non-GAVE, n (%) (n=206)*	p value
ANA	12/18 (67)	174/195 (89)	0.02
Nucleolar ANA	5/15 (33)	26/172 (15)	0.04
Anti-centromere	6/19 (32)	88/179 (49)	0.14
Anti-Scl-70	3/18 (17)	37/186 (20)	1
Anti-U1-RNP	2/16 (13)	15/150 (10)	0.67
Anti-RNA polymerase III	10/14 (71)	16/86 (19)	<0.01
Anti-PM-Scl	1/7 (14)	7/81 (9)	0.50

* Percentages of each autoantibody are calculated as a proportion of patients within each group who have been tested for the given autoantibody

Table 3:

Autoantibody patterns of each GAVE patient

Patient	ANA	Nucleolar ANA	Anti-centromere	Anti-Scl70	Anti-U1-RNP	Anti-RNA Polymerase III
1	–	–	–	–	–	–
2	–	–	–	–	–	+
3	+	+	–	–	–	*
4	+	–	–	+	+	–
5	+	+	–	+	–	+
6*	+	+	+	+	–	*
7	–	–	–	–	–	+
8	+	–	–	–	–	+
9	*	–	–	–	+	+
10**	+	+	–	–	–	*
11	+	–	+	–	–	*
12	–	–	–	–	*	+
13	+	+	–	–	–	+
14	+	–	–	–	–	+
15	+	–	+	*	*	*
16	–	–	+	–	–	+
17	+	–	+	–	–	–
18	+	–	+	–	–	*
19	–	–	–	–	*	+

+ indicates positive autoantibody

– indicates negative autoantibody

* indicates unknown value

* Patient died of respiratory failure due to interstitial lung disease and metapneumovirus.

** Patient died of metastatic non small cell lung cancer and pulmonary hypertension.

Table 4:

Multivariate Logistic Regression

Autoantibody	OR for GAVE (95% CI)	p value
Analysis among all patients (n=225)		
Anti-RNA polymerase III, positive vs negative	10.98 (2.97 – 40.63)	<0.01
ANA, negative vs positive	3.30 (0.97 – 11.23)	0.06
Analysis among all patients with multiple imputation (n=225)		
Anti-RNA polymerase III, positive vs negative	4.57 (1.57 – 13.23)	<0.01
ANA, negative vs positive	3.75 (1.21 – 11.62)	0.02
Analysis excluding patients with missing anti-RNA polymerase III (n=125)		
Anti-RNA polymerase III, positive vs negative	10.11 (2.54 – 40.31)	<0.01
ANA, negative vs positive	5.65 (1.35 – 23.66)	0.02
Analysis among patients with positive anti-RNA polymerase III (n=26)		
ANA, negative vs positive	18.75 (1.68 – 209.54)	0.02
Analysis among patients with negative anti-RNA polymerase III (n=74)		
ANA, negative vs positive	1.70 (0.16 – 17.86)	0.66