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ORIGINAL ARTICLE

The misclassification of gastric antral vascular ectasia

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Abstract

Background: Gastric antral vascular ectasia (GAVE) is characterized by angiodysplastic lesions and is a rare form of gastrointestinal bleeding. Given the multiple patterns, GAVE can be misclassified.
Aim: We analyzed the misclassification of GAVE among patients undergoing esophagogastroduodenoscopy (EGD).
Methods: We performed a retrospective review of 941 EGDs between 2017 and 2019. Inclusion criteria included findings of GAVE on EGD±biopsy. Correct classification was based on visual EGD findings. Outcome variables included misclassification rate, endoscopist's background, and concordance between EGD and pathology. Cohen's Kappa test was used for concordance analysis.
Results: A total of 110 patients had EGD findings of GAVE with a corresponding 184 EGDs. The misclassification rate among EGDs was 74/184 (40%). Furthermore, 81/110 patients were correctly classified with their first workup, whereas 29/110 patients needed repeat testing. In cases of misclassification, GAVE was mostly referred to as erythema (43%), with ulceration, gastritis, or polyps. Sixty-six (60%) patients had biopsies with a concordance of 76% between EGD and biopsy (κ=0.35).
Conclusions: Our findings indicate GAVE was misclassified up to 40% on EGDs with hepatologists and gastroenterologists having similar misclassification rates. Proper identification is crucial given susceptibility to upper gastrointestinal bleeding.
Relevance for Patients: This study emphasizes the importance of accurate classification of GAVE to ensure proper treatment of these lesions which can improve clinical outcomes.

1. Introduction

Gastric antral vascular ectasia (GAVE) is a disease that manifests as vascular lesions within stomach tissue. This disease, when recognized, often presents with melena and iron deficiency anemia secondary to chronic blood loss. Reports have indicated that GAVE represents ~4% of non-variceal upper gastrointestinal bleeding (UGIB) [1,2].

GAVE is often diagnosed on esophagogastroduodenoscopy (EGD) analysis with multiple reported patterns over the past few decades. Among these variations, "watermelon stomach" was a term used to describe the classic appearance of GAVE which is illustrated as red, vascular spots spiraling away from the pylorus (Figure 1) [3,4]. "Honeycomb stomach" is another reported pattern of GAVE represented by the similar red lesions spread out in a diffuse pattern (Figure 2) [4,5]. More recently, a third endoscopic phenotype of GAVE consisting of nodules has been reported (Figure 3). Nodular GAVE is often indistinguishable from other benign antral nodules and may require biopsy for diagnosis [6-8].

GAVE is primarily present in the antrum of the stomach but can also be found in the proximal stomach and cardia as well as in the duodenum, jejunum, and rectum [9]. On

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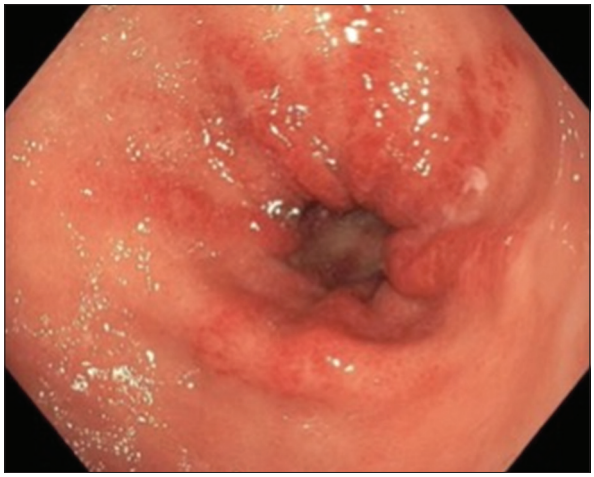

Figure 1. Watermelon pattern.

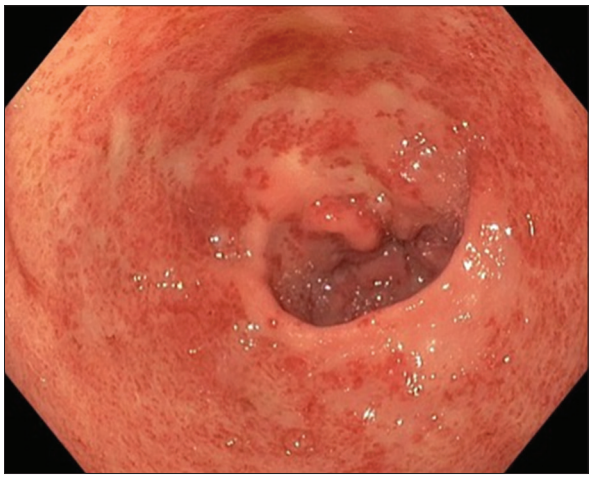

Figure 2. Honeycomb pattern.

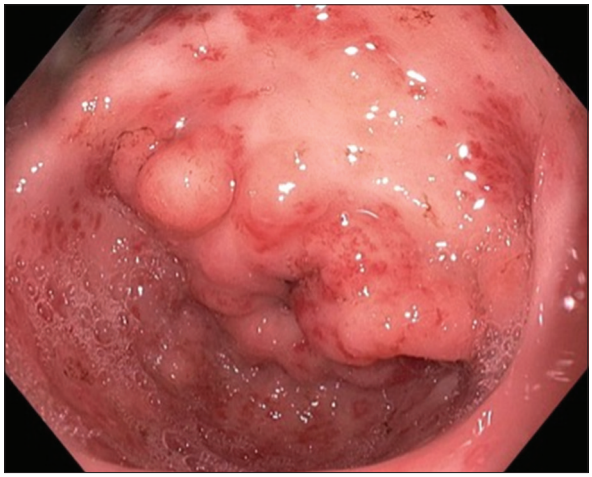

Figure 3. Nodular pattern.

histologic analysis, all three phenotypic variants have characteristic reactive epithelial hyperplasia and vascular ectasia, with more specific findings including smooth muscle, microvascular thrombi, and fibrohyalinosis having variable frequencies of presentation depending on phenotype [8]. The distribution of different clinical presentations and disease associations as a function of specific GAVE phenotypes remains under investigation.

Given the various clinical phenotypes of GAVE, this gastric disease can be misclassified as other entities including erythema, ulceration, gastritis, or polyps in a variety of clinical circumstances. In situations of uncertainty, pathology data may be helpful to aid in proper diagnosis. We aimed to assess the extent to which GAVE was misclassified at a tertiary, academic medical center.

2. Material and Methods

2.1. Study design and patient population

A retrospective chart review was conducted on 941 EGDs performed between 2017 and 2019 at the University of Alabama at Birmingham. The EGDs were further narrowed using a query system within the medical record by searching for "GAVE," "watermelon stomach," and "honeycomb stomach" in EGD or biopsy findings. Pathology data were also filtered by searching for "foveolar hyperplasia," "GAVE," "fibrin thrombi," and "fibromuscular hyperplasia." Inclusion criteria consisted of patients with findings of GAVE on EGD±biopsy. Those without GAVE and those with any other form of upper GI pathology were excluded from the study.

All EGDs were performed by board-certified gastroenterologists or hepatologists. The primary diagnosis of GAVE was determined based on visual EGD findings. Biopsy data were used alongside visual findings to confirm the diagnosis in applicable clinical settings. Misclassification and misdiagnosis were both defined as labeling culprit lesions as other entities (erythema, gastritis, polyps, etc.) despite these lesions actually representing GAVE. The final proper diagnosis of GAVE was verified by two separate board-certified gastroenterologists/hepatologists after reclassification of all the EGD findings.

2.2. Data collection

For the data collection process, all data were taken from the electronic medical record and stored in a secure, de-identified spreadsheet. Baseline demographic data, including age, race, sex, and BMI, were collected on all patients. EGD data were collected on the location and characteristic findings of GAVE as well as the descriptive terminology used to characterize GAVE lesions. Inpatient versus outpatient EGD environments as well as hemoglobin before EGD were also recorded. The total number of EGDs a patient received up until achieving the proper diagnosis was also recorded in addition to the specialty of the endoscopist performing the procedure. EGD images of those initially lacking a specific-labeled pattern of GAVE were later re-examined by board-certified gastroenterologists and hepatologists, where they were labeled a specific pattern. Interventions during the procedure in the form of endoscopic band ligation (EBL) were recorded. Biopsy data from the EGD were also collected.

2.3. Statistical analysis

Demographic information as well as baseline clinical characteristics and descriptive EGD data were represented as a mean±standard deviation for continuous variables and as a

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frequency percent for categorical variables. Misclassification rate was calculated through EGD data by assessing the number of consecutive EGDs required to come to the proper visual diagnosis of GAVE. Biopsy data were also used alongside EGD findings to help confirm diagnosis. Chi-squared test was implemented to compare any significant differences between EGD characteristics based on the specialist performing the procedure (gastroenterologist versus hepatologist). Cohen's Kappa test for interrater reliability was also utilized to measure the overall concordance between visual diagnosis of GAVE on EGD and biopsy findings. A kappa score (κ) <0.5 points toward a lack of consistent agreement [10]. All the analysis was conducted using SAS 9.4 (Cary, NC).

3. Results

3.1. Patient demographics

The entire cohort consisted of 110 patients who were diagnosed with GAVE at some point along the study period, of which a consecutive total of 184 EGDs were performed. Our population had 60 females (55%) with an average age at the time of each patient's first EGD being 58.91±9.92 years. The distribution or race included 102 (93%) Caucasian patients and 8 (7%) African American patients with an average BMI at first EGD being 31.86±8.59. There were 90 (82%) patients with cirrhosis, 28 (25%) patients with chronic kidney disease (CKD), and 13 (12%) patients with end stage renal disease (ESRD) on hemodialysis. Some patients had multiple comorbidities in that there were 28 patients with both CKD and cirrhosis, while there were 11 patients with both ESRD and cirrhosis.

3.2. EGD diagnostic data

Out of the total 184 EGDs that were analyzed, 74 (40%) had failed to classify the culprit lesions as GAVE, and 110 (60%) correctly classified these lesions as GAVE. A minority (47/184, 26%) of these EGDs were inpatient with average hemoglobin at the time of EGD being 10.25±7.88 g/dL. From an individual patient perspective, 81/110 (74%) of our total patients were diagnosed during their first workup (EGD±biopsy), whereas 29/110 (26%) required multiple EGDs to come to the correct diagnosis of GAVE (Table 1). The correct EGD visual classification of GAVE was eventually achieved in 100% of our patients following multiple consecutive EGDs following lack of diagnostic clarity and persistence of clinical symptoms (anemia, bleeding) in certain patients. During the EGD itself, active bleeding was visualized on the GAVE lesions only 26 (14%) of the cases.

A breakdown of the subtypes of GAVE seen within our series of patients include 22 (20%) nodular, 17 (16%) watermelon, 3 (3%) honeycomb, and 4 (3%) mixed. The remaining 64 (58%) patients were not given a GAVE subtype classification due to the endoscopists failure to report a pattern or failure to recognize a GAVE pattern initially during the EGD. Among these 64 patients whose GAVE subtype was initially not specified, subtypes were later labeled as watermelon (*n*=28, 44%), honeycomb (*n*=24, 38%), nodular 10 (*n*=15%), honeycomb + nodular (*n*=1, 1.5%), and watermelon + nodular (*n*=1, 1.5%).

EBL was performed on 12 (11%) patients total with the nodular subtype taking up an overwhelming majority of these interventions: 9/22 (41%) nodular, 2/4 (50%) mixed nodular, and 1/64 (2%) unclassified. The majority of GAVE in our patient population were seen only in the antrum (77%). The remaining patients (23%) had GAVE in the antrum in addition to other areas including the body (*n*=3), cardia (*n*=3), duodenum (*n*=10), pylorus (*n*=2), and a mixture of multiple (≥3) sites (*n*=7).

3.3. EGD misclassification and pathology concordance

In instances of misclassification, "erythema" was the most used word to characterize GAVE with 15/74 (20%) instances of erythema used as a stand-alone term and 17/74 (23%) instances of erythema used in combination with other descriptive terms including erosion (n=4), gastritis (*n*=3), inflammatory polyp (*n*=6), nodularity (*n*=1), and ulceration (*n*=3). Other descriptive terminology used in instances of misclassification included duodenopathy 15/74 (20%), inflammatory polyp 14/74 (19%), portal hypertensive gastropathy 2/74 (3%), gastritis 6/74 (8%), erosion 2/74 (3%), and a combination of ulcer with erosions 3/74 (4%). Descriptive EGD data are depicted in Table 2.

Gastroenterologists misclassified GAVE on EGD at a rate of 47% compared to hepatologists who misclassified GAVE on

Table 1. Baseline patient data

Variable	Patient data (*n*=110)
Age, mean±SD	58.91±9.92 years
Sex, *n* (%)	
Male	50 (45%)
Female	60 (55%)
Race, *n* (%)	
Caucasian	102 (93%)
African American	8 (7%)
BMI, mean±SD	31.86±8.59
Number of EGDs required for GAVE diagnosis, *n* (%)	
1 EGD	81 (74%)
>1 EGD	29 (26%)
GAVE subtypes, *n* (%)	
Nodular	22 (20%)
Watermelon	17 (16%)
Honeycomb	3 (3%)
Mixed	4 (3%)
Unlabeled	64 (58%)
GAVE locations, *n* (%)	
Antrum	85 (77%)
Antrum+Duodenum	10 (9%)
Antrum+Body	3 (3%)
Antrum+Cardia	3 (3%)
Antrum+Pylorus	2 (2%)
Antrum+Multiple other locations	7 (6%)
Biopsy performed	60 (55%)
EVL performed	12 (11%)

SD, standard deviation.

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EGD at a rate of 37%, with no statistically significant difference in misclassification rate (P=0.22). These misclassification rates were calculated based on different consecutive EGD cases. There were 66 (60%) patients who received a biopsy during EGD. The concordance and discordance rates between EGD and biopsy findings were 50/66 (76%) and 16/66 (24%), respectively. Cohen's Kappa test for interrater reliability depicted a value of κ=0.35 indicating poor agreement overall (Table 3).

4. Discussion

GAVE is a rare cause of UGIB that can be difficult to recognize given the different characteristic lesions that may be confused for erythema, ulcers, gastritis, or polyps. We studied the misclassification of GAVE at a tertiary academic medical center where in the span of a 3-year period, GAVE was failed to be recognized in up to 40% of consecutive EGDs. This translated to almost 30% of patient's failing to have their culprit lesions classified as GAVE on their first EGD with the remaining patients requiring further EGDs before coming to correct classification. During instances of misclassification, GAVE was most frequently mistaken for erythema, duodenopathy, and inflammatory polyps. Hepatologist had a misclassification rate of 37% which was lower than the gastroenterologist misclassification rate of 47%. GAVE often presents in cirrhotic patients [11] making hepatologists likely more familiar with the appearance of GAVE as it is more prevalent in their patient population. The prevalence of cirrhosis in our cohort was 82%. Over half of the patients in our cohort (60%) received a biopsy of their gastric lesions at a certain point along their clinic course which aided in confirming GAVE diagnosis. The overall concordance rate between visual EGD findings and pathology data was 76% with a κ=0.35 following interrater reliability testing. These values suggest lack of consistent diagnostic agreement between gastric EGD findings and corresponding biopsy data [10].

Table 2. GAVE misclassification trends on EGD

Variable	EGD data (%)
GAVE classification, *n* (%)	
EGD classification	110 (60)
EGD misclassification	74 (40)
Misclassification terms, *n* (%)	
Erythema	15 (20)
Erythema+Erosion	4 (5)
Erythema+Gastritis	3 (4)
Erythema+Inflammatory Polyp	6 (8.5)
Erythema+Ulceration	3 (4)
Erythema+Nodularity	1 (1)
Duodenopathy	15 (20)
Inflammatory polyp	14 (19)
Gastritis	6 (8.5)
Portal hypertensive gastropathy	2 (3)
Erosion	2 (3)
Erosion+Ulcers	3 (4)
Endoscopist misclassification, *n* (%)	
Gastroenterologist	27 (47)
Hepatologist	46 (37)

Table 3. Contingency tables with concordance between EGD and pathology data

GAVE on EGD	GAVE on biopsy	
	No	Yes
No	7	1
Yes	15	43

κ=0.35 indicating poor agreement

Given the unclear pathophysiologic mechanism as well as the emerging associations with different conditions and disease, GAVE has remained a challenging disease for both diagnosis and management for several years [12]. The primary diagnosis of GAVE is achieved by accurate classification of EGD visual findings; however, pathology data have served useful to aid in diagnosis alongside EGD findings. A scoring system known as the "Gilliam score" was created early on to aid in histologic diagnosis of GAVE. This scoring system focused on the following criteria: spindle cell proliferation presenting with either ectasia, fibrin thrombi, or a combination of both ectasia and fibrin thrombi [13]. Payen *et al.,* further, expanded this scoring system to include fibrohyalinosis as a third diagnostic criteria for GAVE. This more robust score was referred to as the "GAVE score" [9,14]. The GAVE score has three criteria and is a 5-point score. Fibrin thrombi and/or vascular ectasia are the first criteria, for which one point is given to only one being present, and two points are given to both being present. Spindle cell proliferation is the second criterion, for which one point is given for increased proliferation and two points are given for marked increased proliferation. The third criterion is fibrohyalinosis, where 1 point is given for the presence of fibrohyalinosis. A GAVE score ≥3 has been deemed to be the best indicator of GAVE on biopsy [9,14].

Although biopsy may be helpful in certain scenarios, it should not be used as a sole measure for GAVE diagnosis given its high false negative rate [13]. If biopsy had been implemented in the 65 cases that did not receive biopsy and were not classified as GAVE on initial EGD, a significant proportion of these biopsied lesions would likely have resulted negative for GAVE. This would be secondary to the high false negative rate as well as the patchy area of distribution of the lesions themselves. Therefore, biopsy should only be instituted in situations to confirm the diagnosis of clinically suspicious GAVE lesions on EGD.

GAVE can often be confused with portal hypertensive gastropathy based on EGD findings, as was the case for a small number of our patients. The 30% prevalence of GAVE in cirrhotics can further add to this confusion [11]. Even though portal hypertensive gastropathy is typically more prominent in the fundus or corpus, endoscopists can still confuse the two conditions for one another [14,15]. These two entities can be differentiated histologically by use the of the GAVE score, where a score ≥3 is highly suggestive of GAVE. Discriminant analysis depicted spindle cell proliferation with fibrohyalinosis to maintain a diagnostic accuracy of 85% for GAVE when compared to portal

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hypertensive gastropathy [14]. Furthermore, therapeutic strategies and maneuvers to reduce portal pressure, including beta blockers, somatostatin analogues, transjugular intrahepatic portosystemic shunt placement, and portocaval shunt surgery, are only effective for treatment of portal hypertensive gastropathy and will not improve GAVE lesions [16].

Among the three GAVE subtypes, nodular GAVE is the most often misdiagnosed. This pattern often can be indistinguishable from benign antral nodules of multiple origins including epithelial hyperplasia, reactive gastritis, and inflammatory pancreatic heterotopia [8]. Almost 30% of our misclassified, patients had GAVE misrepresented as inflammatory polyps. Such confusion may lead to delays in treatment [17]. It is in these instances that biopsy can be helpful for diagnosis. With only 60% of our patients receiving biopsies, diagnosis rates may improve with more frequent biopsies in clinically suspicious lesions. Pathology findings, however, should be used with caution as GAVE findings may still be indistinguishable from gastritis or normal gastric mucosa on microscopic analysis [18]; therefore, we reiterate that the diagnosis of GAVE is primarily a visual diagnosis where pathological findings can be applied for confirmation in the proper clinical situation. Any maneuvers geared toward clear visualization of the antrum will aid in the visual diagnosis of GAVE. It is important that the ideal amount of air insufflation is applied to prevent either over insufflation or under insufflation to therefore achieve clear view of the antrum and the remainder of the stomach [19]. The high percentage of originally unspecified GAVE subtypes in our study (58%) indicates that even in instances of classification, identifying pattern subtype was not prioritized. Standardized visual EGD criteria for diagnosis may improve such measures.

As we highlight the misclassification of GAVE, we recognize our study has limitations. Our study is limited in its retrospective design, limited sample size, and single center experience. Our study setting being at an academic teaching hospital may not be representative of a similar trend seen out outside non-academic institutions without residents and fellows. Regarding pathology data, one must comment on the possibility of a target biopsy, leading to selection bias or sampling the incorrect area. Moreover, our conclusion on the misclassification of GAVE based on endoscopists specialty is limited in that our comparison is based on different EGD cases rather than identical EGD cases among these specialists.

Our study illustrates that the diagnosis of GAVE can be challenging given the possibility of resembling other forms of gastric lesions on EGD. Both board certified gastroenterologists and hepatologists struggled with EGD classification of GAVE in certain instances. These findings assert that the diagnosis of GAVE requires a multifaceted approach revolving around clinical presentation, visual EGD findings, and pathology data for confirmation in situations of uncertainty. In addition, GAVE visual classification may require further emphasis for trainees and current practitioners moving forward.

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Conflict of Interest

None of the authors have any conflicts of interest to declare.

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