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STOMACH AND DUODENUM (J PISEGNA AND J BENHAMMOU, SECTION EDITORS)

Gastric Antral Vascular Ectasia Pathogenesis and the Link to the Metabolic Syndrome

Elliot Smith[1] · Jessica Davis[1] · Stephen Caldwell[1]

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Abstract

Purpose of Review Gastric antral vascular ectasia (GAVE) is a well-described source of chronic blood loss. We aim to review the previously hypothesized etiologies of GAVE and focus on recent proposed mechanisms, including metabolic syndrome. We will support these theories with newly discovered clinical associations and possible therapeutic implications.

Recent Findings Historically, GAVE has been associated with connective tissue disease and liver disease. Based on these associations and its histologic appearance, GAVE has presumed to be caused by mechanical- and hormonally mediated injury. Recent findings have been notable for a clinical association with aspects of the metabolic syndrome. Therefore, the pathogenic etiology may be akin to aspects of the metabolic syndrome via microvascular injury and neoangiogenesis.

Summary The potential etiologies of GAVE include hypergastrinemia, mechanical injury, and microvascular injury with neovascular proliferation particularly in the metabolic syndrome. Further research is needed to evaluate these proposed mechanisms and potential targets for treatment.

Keywords GAVE · Gastric antral vascular ectasia · Metabolic syndrome · Pathophysiology · Motility · Gastrin

Introduction

Gastric antral vascular ectasia (GAVE) is a disease process in the stomach typically presenting with chronic blood loss and iron-deficiency anemia. It has been reported to account for 4% of all upper non-variceal gastrointestinal bleeding, and up to 62% of patients afflicted with the disease become transfusion dependent [1, 2]. GAVE was first described in the literature by Rider et al. in 1953 [3]. It did not become widely recognized until the advent of modern endoscopy, however, and was first characterized in detail by Jabbari et al. in 1984. This case series described three patients with "classic" features of endoscopic GAVE, characterized by longitudinal streaks of erythematous mucosa. The term "watermelon stomach" was coined based on this striped appearance [4••]. An association with metabolic syndrome has only become apparent in recent years [5, 6••, 7]. Below, we offer a detailed historical perspective on the pathogenesis of GAVE and a perspective on its relationship to vascular changes in metabolic syndrome which is emerging as a more significant association.

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✉ Stephen Caldwell
shc5c@virginia.edu

[1] Division of Gastroenterology and Hepatology, University of Virginia, JPA and Lee St., PO Box 800708, Charlottesville, VA 22908-0708, USA

Background

Once thought to be a rare disease, the diagnosis of GAVE has become more common with recent prevalence estimates of up to 14% in the cirrhotic patient population [8]. Since its original description, three endoscopically recognized phenotypes have been described, which may also present in combination. These phenotypes include the following: (1) the "classic" striped "watermelon" appearance, which can be raised or flat; (2) a diffuse antral distribution of scattered angiodysplasias, occasionally referred to as a "honeycomb" pattern; and (3) a nodular variant also known as nodular antral gastropathy or NAG [9–12]. In addition to antral disease, GAVE can also manifest with a patch in the proximal cardia. Cardial involvement may be seen in up to 41% of patients with GAVE and is frequently associated with a diaphragmatic hernia [13•, 14].

The histological diagnosis of GAVE is confirmed by the presence of abnormally dilated mucosal vessels with fibrin

thrombi, spindle cell proliferation, and fibromuscular hyperplasia in the lamina propria [15, 16]. Histology can assist in differentiating GAVE from portal hypertensive gastropathy (PHG). Specifically, the presence of increased spindle cell proliferation and "fibrohyalinosis" is more frequently noted in GAVE [17]. However, histologic confirmation is not routinely indicated as endoscopic diagnosis has excellent interobserver agreement [8]. In addition, histologic evaluation can yield a false-negative result from inadequate sampling and may require special stains for microthrombi (CD61) to confirm the diagnosis [18, 19]. Lastly, histology cannot distinguish GAVE from hyperplastic polyps; nodular GAVE could therefore easily be misdiagnosed as a hyperplastic polyp [20].

GAVE is thought to be an acquired disease based on its histologic findings and average age of incidence [13•, 16]. The first epidemiologic descriptions of GAVE were in the 1980s and 1990s, at which time GAVE was noted to have a female predominance with average age of diagnosis in the eighth decade of life. In addition, there appeared to be a clear association with autoimmune connective tissue disease, liver disease, ischemic heart disease, chronic kidney disease, and bone marrow transplantation [11, 13•, 17, 21].

Clinical associations have since expanded to include many components of the metabolic syndrome including obesity, diabetes mellitus, non-alcoholic steatohepatitis (NASH), chronic kidney disease (CKD), hypertension, and hyperlipidemia [5, 6••, 7]. Various treatment options have been proposed for the management of GAVE, which include but are not limited to thermal ablation, cryotherapy, band ligation, radiofrequency ablation, and hormonal therapy [22–26]. In this review, we will focus on proposed pathophysiologic etiologies and potential treatment modalities of GAVE, beginning with historical associations and concluding with associations with metabolic syndrome.

Portal Hypertension

Given its association with advanced chronic liver disease and resolution after liver transplantation, GAVE has been thought to be potentially related to portal hypertension [27, 28]. A few retrospective series have suggested that GAVE, unlike PHG, is not driven by portal pressures. Two of these case series evaluated patients with GAVE and transfusion requirements who underwent portosystemic shunting, most commonly via transjugular intrahepatic portosystemic shunt (TIPS) [29, 30]. Despite successful reductions in the portosystemic gradient after shunting, both groups found no improvement in the endoscopic appearance of GAVE and no reduction in the need for transfusion support post-intervention. In an effort to parse the effect of reductions in portal pressure from improvement in liver function after liver transplantation, Vincent et al. published an elegant report of two patients with GAVE who underwent liver transplantation but had persistent portal hypertension post-transplant [31]. Both patients in this series had GAVE requiring transfusion support prior to transplantation. Both also had portal venous thrombosis requiring portocaval anastomosis during transplant that resulted in ongoing portal hypertension after transplant, evidenced clinically by persistent post-operative ascites, splenomegaly, and thrombocytopenia. Despite this continued portal hypertension, both patients were noted to have endoscopic improvement of GAVE and no longer required serial transfusion, suggesting that the benefit of transplant for GAVE is independent of portal pressure. While these studies are small, each indicates that, in contrast to PHG, portal hypertension does not play a significant role in GAVE.

Mechanical Stress as a Pathogenic Mechanism in the High-pressure Antral "Grinder"

Many authors have explored the idea that GAVE could be related to mechanical stress in the high-pressure antral "grinder" which converts partially digested food to intestinal chyme. In the initial case series characterizing GAVE, Jabbari et al. noted that one patient had antral prolapse visible on antrectomy, suggestive of a mechanical cause for the mucosal lesions they observed [4••]. The aforementioned distinctive histologic findings of GAVE—dilated mucosal vessels with occasional microthrombi and fibromuscular obliteration of the lamina propria—are similar to histologic findings in other types of traumatic intestinal injury such as intussusception, solitary rectal ulcers, and rectal prolapse. The characteristic linear appearance of GAVE involving the tops of mucosal folds is also suggestive of a mechanical element in that these regions would be the most vulnerable to injury during contraction [16]. Antral motility in cirrhosis patients with GAVE has been observed by ultrasound to be different than in cirrhosis patients without GAVE, suggesting a potential mechanism for this injury [32]. In addition, gastrointestinal motility disorders are commonly found in many of the diseases associated with GAVE including cirrhosis, ESRD, scleroderma, and DMII [6••, 33–35]. GAVE patients have been noted to have concurrent vascular ectasias in the cardia as well as the antrum, another relatively high-pressure region in the stomach, leading authors to suggest restricted blood flow in these regions could contribute to the dilation of superficial vessels seen in GAVE [13•, 14]. More nuanced study of antral motility in cirrhosis patients is needed to better explain the role of mechanical stress in GAVE.

Hormones

A hormonal mechanism of injury has been discussed extensively in the GAVE literature. The association with liver disease and ESRD would suggest that there are substances not readily cleared by these organs that lead to GAVE. Gastrin, glucagon, and nitric oxide in particular have been posited as candidates that are "increased in patients with severe cirrhosis and normalize after transplantation" [31]. ESRD has also been associated with hypergastrinemia as well as elevations in 5-hydroxytrypamine and vasoactive intestinal peptide (VIP). Quintero et al. described a case series in which 8 of 11 cirrhotic patients with GAVE had hypergastrinemia, while 7 of 11 had low levels of serum pepsinogen I [36]. Gostout et al. also reported in a case series of 33 patients tested for gastrin that 25 (76%) had elevated levels, of which 14 had a concomitant diagnosis of pernicious anemia [13•]. Case reports of improvements in GAVE-associated bleeding with the use of octreotide, a somatostatin analog that inhibits gastrin, lend further credence to this theory [24, 37]. There have also been reported cases of improvement with the removal of proton pump inhibitors (PPI), theoretically due to a mitigation of the hypergastrinemic state that is associated with the use of these agents [37, 38]. PPIs may also promote mechanical injury, as gastric acid suppressants are known to slow gastric emptying and increase antral contractility [39]. Lastly, GAVE and hyperplastic polyps share similar histologic features as well as a clinical association with autoimmune gastritis and elevated gastrin levels, perhaps suggesting a shared mechanism [40–42].

Hypergastrinemia has not always been found to be associated with GAVE, however. In a comparative study of 24 patients with cirrhosis, 14 with GAVE and 10 without GAVE, low levels of serum gastrin were noted in both groups, militating against hypergastrinemia as a governing mechanism for this process [17]. Lowes et al. described the histopathologic findings in a patient who underwent antrectomy for GAVE in 1989 [43]. This was notable for the presence of "intraepithelial and extraepithelial neuroendocrine proliferations that contained large quantities of the known vasodilators 5-hydroxytrptamine and vasoactive inhibitory peptide." The authors suggested that these findings may have been downstream effects of hypergastrinemia or chronic inflammation, though this hypothesis has not been further investigated. Still other hormonal hypotheses have been suggested by, for example, a case report of a patient with GAVE successfully treated with cyproheptadine, a serotonin antagonist; and separate findings of increased biosynthesis of prostaglandin E2 in cirrhotic patients with GAVE, suggesting its potential role in mediating injury via vasodilation and acid inhibition [44, 45].

Connective Tissue Disease

Autoimmune disease, and specifically connective tissue disease, has been found to be associated with GAVE, accounting for 14.8 to 62% of all patients with this diagnosis in some series [6••, 13•]. In a report of 103 patients with severe diffuse systemic scleroderma (SSc), 23 (22.3%) were noted to have GAVE on screening EGD. The patients with GAVE were also found to have ectasias outside of the antrum in 26% of cases and were at increased likelihood of decreased pulmonary diffusion capacity (DLCO). On the basis of these findings, the authors suggested that GAVE in the scleroderma population may represent an immune-mediated vasculopathy [46]. Other studies in this patient population have noted an increased association with cutaneous telangiectasias with similar histologic features to GAVE, including small vessel dilation with fibrin deposition [47, 48]. Initial reports suggested that decreased anti-topoisomerase I titers and increased anti-RNA polymerase III titers may confer a higher risk of GAVE in patients with scleroderma; however, this was not reproduced on further evaluation [46, 47]. The successful treatment of patients with SSc and refractory GAVE with cyclophosphamide and/or steroids has been reported multiple times in the literature [46, 49–51]. Although the exact immune target is unclear, such reports bolster the theory that some forms of GAVE may represent an immune-mediated process.

Tyrosine Kinase Inhibitors

Over the last few years, there have been new reports of GAVE associated with the use of tyrosine kinase inhibitors (specifically imatinib and dasatinib) for the treatment of neoplastic processes. The endoscopic appearance of GAVE has reliably resolved after these agents are discontinued [52•, 53–56]. Imatinib and dasatinib are tyrosine kinase inhibitors that are used widely in the treatment of CML by inhibiting cells containing the BCR-ABL protein. These chemotherapies also inhibit the c-KIT and PDGFRA tyrosine kinases, which are gain of function proteins that are targeted in GISTs [57–59]. Interstitial cells of Cajal are presumed to be the precursor cells of GISTs and would therefore likely be impaired, leading to altered gastrointestinal motility, another putative risk factor for GAVE [60–62].

Metabolic Syndrome: an Emerging Link With GAVE

Reports of the clinical associations of GAVE initially focused primarily on cirrhosis and connective tissue disease. In recent years, there has been increased evidence of associations

between GAVE and various features of the metabolic syndrome. These associations include obesity, diabetes, NASH, hypertension, and hyperlipidemia [5, 6••, 7]. We reported a retrospective review of 135 patients with GAVE, of whom 64% had diabetes, 28% had NASH, and the average body mass index (BMI) was 33.7. We did not find an association with autoimmune disease [6••]. A similar chart review was performed in a separate cohort of 109 patients, of whom the average BMI was 34, and 58% had diabetes [5]. These clinical associations may confer an increased risk of gastrointestinal motility disorders, leading to a theoretical mechanism for GAVE as previously discussed. However, another proposed mechanism is related to particular pathophysiology of the metabolic syndrome.

The metabolic syndrome is a heterogeneous group of disorders associated with an increased risk of insulin resistance, cardiovascular disease, and type II diabetes mellitus. There are many definitions that have been put forward by national and international health organizations, the majority of which include central obesity, hypertension, hyperlipidemia, and elevated fasting glucose [63, 64]. Other disease processes have been found to be associated with metabolic syndrome, including NASH, CKD, and polycystic ovary syndrome [65–67]. The pathogenesis of disease sequelae related to metabolic syndrome, including GAVE, is not entirely clear, but current models favor their arising from a background pro-inflammatory, pro-thrombotic, oxidative state [63, 64, 68]. In addition, patients with frank diabetes may precipitate direct microvascular injury in a similar fashion to other more well-known end-organ complications, such as diabetic retinopathy and nephropathy. It has been proposed that cellular injury occurs from increased osmotic stress from cellular sorbitol accumulation. This leads to a relative hypoxic state and a subsequent increase in VEGF, promoting vascular proliferation [69].

In a prospective study of 27 patients with GAVE and 11 controls, Tekola et al. demonstrated a decrease in relative vascular flow between the antrum and gastric body in the GAVE patients as measured by endoscopic laser Doppler flowmetry [70]. This finding suggests that although GAVE can cause active GI bleeding, the underlying vascular state may be one of hypoperfusion, which would also correspond to a relative hypoxic state. A low-flow, pro-inflammatory, and oxidative state could also putatively lead to the micro-thrombi and vascular ectasia (as a function of neovascularization) noted on histology. There may also be crossover with SSc, as it has been suggested that the various manifestations of SSc are primarily mediated by microvascular injury and VEGF upregulation [71].

Supporting this hypothesis of injury and neoangiogenesis at the microvascular level is evidence of the successful treatment of GAVE with VEGF inhibitors in a similar fashion to diabetic retinopathy [72]. There have been three cases reported in the literature of GAVE refractory to argon plasma coagulation (APC) that were successfully treated with thalidomide, a potent anti-VEGF agent. Two of these cases reported serum VEGF levels that decreased dramatically with treatment [73, 74]. As previously discussed, GAVE has been successfully treated with the use of octreotide, which, in addition to decreasing gastrin levels, is also noted to suppress multiple growth factors linked to angiogenesis [24].

Conclusion

GAVE is a chronic process affecting the stomach that can lead to persistent blood loss and significant morbidity. The phenotypes of disease include the classic striped appearance, a diffuse "honeycomb" pattern and a nodular polypoid form. As described in Fig. 1, there are a wide variety of diseases associated with GAVE including cirrhosis, connective tissue disease, diabetes, obesity, and chronic kidney disease. Given these heterogeneous phenotypes and clinical associations, it is most likely that there are multiple pathophysiologic mechanisms leading to similar clinical manifestations. These mechanisms include hypergastrinemia, mechanical injury, and

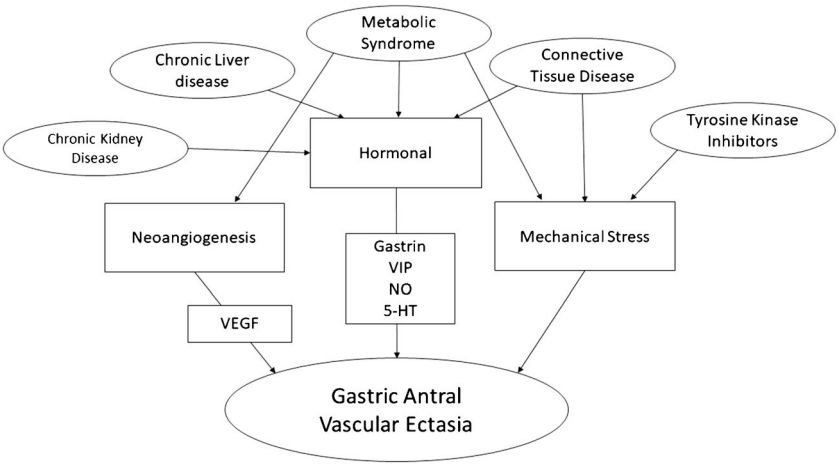

Fig. 1 Proposed etiologies of gastric antral vascular ectasia

microvascular injury with neovascular proliferation. While endoscopic therapies have been found useful to mitigate bleeding, future investigation should be aimed at systemic interventions addressing the underlying etiology, particularly in cases refractory to endoscopic management. Such approaches include therapy directed at hypergastrinemia, antral contractility, microvascular injury, or neoangiogenesis. The effects of better controlling metabolic syndrome as a strategy to treat GAVE remain to be explored, but the associations suggest that this may warrant further study.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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