

Gastric antral vascular ectasia and end-stage renal disease: literature review

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Summary

Background. Gastric antral vascular ectasia is currently recognized as an important cause of upper gastrointestinal hemorrhage and has a high prevalence in patients with renal insufficiency and end-stage renal disease. It is responsible for about 4% of non-variceal upper gastrointestinal hemorrhages and typically presents in middle aged females. GAVE, also called “watermelon stomach”, is diagnosed through esophago-gastroduodenoscopy and is characterized by the presence of visible columns of red tortuous enlarged vessels along the longitudinal folds of the antrum. The pathogenesis is still obscure and many hypotheses have been proposed such as mechanical stress, humoral and autoimmune factors. In the last two decades, numerous therapeutic strategies have been proposed, including surgical, endoscopic, and medical choices, yet successful treatment of GAVE continues to be a challenge. Currently, given the rapid response, safety, and efficacy, endoscopic ablative modalities have largely usurped medical treatments as first-line therapy, particularly using argon plasma coagulation.

Conclusions. GAVE syndrome is a serious condition and has a higher prevalence in end-stage renal disease patients, especially in those presenting with treatment-refractory anemia. Realization of its etiology and characteristics is essential for doctors to suspect, diagnose, and treat gastric ectasia. Only proper diagnosis and well-timed disease treatment can significantly improve patient’s medical condition and future prognosis.

Keywords: gastric antral vascular ectasia, “watermelon stomach”, end-stage renal disease, hemodialysis complications.

INTRODUCTION

Gastric antral vascular ectasia (GAVE) syndrome, also known as “watermelon stomach”, is involved in 4% of non-variceal upper gastrointestinal bleeding developments [1] and can be a cause of severe blood effusion. The diagnosis is problematic as it can be overshadowed by more frequent bleeding causes like peptic ulcer disease, gastric mucosal erosions, Mallory-Weiss syndrome, gastrointestinal cancer, and other reasons [2]. Clinically, this syndrome often coexists with other disorders [3], such as liver cir-

rhosis, autoimmune connective tissue disorder, bone marrow transplantation, ischemic heart disease, valvular heart disease, hypertension, hypothyroidism, diabetes, or acute myeloid leukemia [4–8]. Recent studies show that end stage renal disease (ESRD) is associated with a high incidence of GAVE syndrome [9]. Therefore, realization of its etiology and characteristics is essential for doctors to suspect, diagnose, and treat gastric ectasia in patients with renal insufficiency, especially in the presence of severe anemia dependent on erythropoietin or red blood cell transfusion therapy.

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HISTORICAL REVIEW

GAVE syndrome was first described by Rider et al. in a patient with severe chronic iron-deficiency anemia and presented as "an erosive type of gastritis with marked veno-capillary ectasia" [10]. In 1984, Jabbari et al. used endoscopic techniques to visualize the alterations with greater detail and defined GAVE syndrome more precisely as "longitudinal rugal folds traversing the antrum and converging on the pylorus, each containing a visible convoluted column of vessels" [11]. These endoscopic appearances were similar to stripes on a watermelon, and he coined the term "watermelon stomach". Columns of ectatic vessels along the longitudinal folds typically limited to the antrum are pathognomonic for GAVE syndrome [12].

EPIDEMIOLOGY

Gastrointestinal bleeding is a serious condition that medical practitioners encounter in the emergency department, as well as in the primary care setting [13]. Upper gastrointestinal bleeding has an overall mortality rate of 6–10% and an annual incidence that ranges from 40 to 150 episodes per 100,000 persons [14–16]. Males aged 61 to 69 are more likely to suffer from this condition compared with other individuals [17]. The most frequent causes of upper gastrointestinal bleeding appear to be peptic ulcer disease (51% (duodenal 34%, gastric 17%)), gastric mucosal erosions (33%), Mallory-Weiss syndrome (4%), gastrointestinal cancer (4%), unidentified (3%), and other (5%) reasons [18]. GAVE syndrome is considered a rare medical condition and accounts for up to 4% of all non-variceal upper gastrointestinal bleedings [1]. Typical initial presentations range from occult bleeding causing transfusion-dependent chronic iron-deficiency anemia to severe acute upper gastrointestinal bleeding [19]. Based on the results of a single-center study of 45 patients, elderly females (average age 73 years) are more susceptible to GAVE syndrome [8]. However, males (average age 65 years) with GAVE syndrome have more prevalent liver cirrhosis (30–66%) [3, 8, 20].

LINK WITH OTHER DISEASES

GAVE syndrome is usually associated with autoimmune conditions and is observed in 62% of autoimmune connective tissue disorder cases [8], 31% of Raynaud's phenomenon cases. Other underlying conditions include systemic sclerosis and CREST (Calcinosis, Raynaud's syndrome, Esophageal dysmotility, Sclerodactyly, and Telangiectasia) [4, 8, 21, 22]. There have been published case reports of GAVE syndrome in patients with bone marrow transplantation, ischemic heart disease, valvular heart disease, hypertension, hypothyroidism, diabetes, and acute myeloid leukemia [3–8]. Some reports also show that GAVE syndrome is present in patients with ESRD [23–28].

PATHOPHYSIOLOGY

The pathophysiology of GAVE syndrome remains unclear mainly because of its low incidence and the lack of controlled studies. Most of the available theories are either based on single case reports or on small studies with 15 or fewer cases and are therefore weakly founded. Nevertheless, having reviewed the relevant literature, we propose to distinguish 3 possible theories: mechanical stress, humoral and autoimmune.

Mechanical stress theory

Several studies have suggested the presence of mechanical stress in the pathogenesis of GAVE syndrome. Strong gastric peristalsis has been supposed to induce prolapse and trauma of antral mucosa and intermittent obstruction of blood vessels leading to fibro-muscular hyperplasia and secondary formation of GAVE syndrome [30]. Charneau et al. found that antral motility time was significantly increased in patients with liver cirrhosis and GAVE syndrome, when compared with healthy controls [31]. Adachi et al. states that uremia in chronic kidney disease (CKD) patients affects the process of gastric emptiness by weakening it, which in turn leads to an increase in mechanical stress of the antrum [29]. This finding supports the idea that mechanical stress plays an important role in the pathogenesis of GAVE syndrome.

Humoral theory

Many authors have assumed a pathogenic importance of humoral factors

like gastrin, vasoactive inhibitory peptide (VIP), 5-hydroxytryptamine, glucagon, catecholamines, prostanoid, and other undefined vasoactive substances [32]. Gastrin is hypothesized to induce spindle cell proliferation, hyperplasia, prolonged sphincter relaxation, and capillary and venous dilatation [32]. GAVE syndrome has been associated with both increased and decreased levels of gastrin, therefore the data about importance of this hormone are very conflicting [30, 33]. The release of VIP, 5-hydroxytryptamine, prostaglandin E2 and prostanoid seems to be responsible for the local vasodilatation; their concentrations were found to be significantly higher in cirrhosis patients with GAVE syndrome than in healthy controls [30, 34, 35]. It has been suggested that impaired renal excretory function and decreased removal of vasoactive substances from the circulatory system may be associated with emergence of gastric vascular ectasia [23–28].

Autoimmune theory

The presence of autoantibodies and autoimmune associated disease has been determined in up to 60% of all patients with GAVE syndrome [8, 19]. Watson et al. describes that patients with systemic sclerosis and GAVE syndrome were positive for antinuclear antibodies, with some positive for anti-centromere antibodies as well [22]. Studies by Garcia et al. and Valdez et al. found that these antinuclear antibodies are produced against a specific enzyme called RNA helicase II [36, 37], they are involved in cell growth, and are a cause of autoimmune reactions [38]. It is thought that various disease combinations such as kidney failure, diabetes, or systemic sclerosis can lead to the initiation of GAVE syndrome.

MORPHOLOGICAL AND HISTOLOGICAL FEATURES

The diagnosis of GAVE syndrome is mainly based on patient's anamnesis and endoscopic appearance, which is the main criterion for positive diagnosis. Lesions are multiple in 40–75% [39–41] of cases and are typically located in the gastric antrum or rarely found in other areas of the gastrointestinal tract, including cardia, duodenum, jejunum, and rectum [42–46]. The involvement of the proximal part of the stomach is rare and generally associated with diaphragmatic hernia [8]. Gastric lesions appear flat or

Table. Differential diagnosis

Feature	Condition	GAVE syndrome	Portal hypertensive gastropathy
Localization		Limited to the antrum	Changes in the fundus and corpus
Morphological features		Reddish vascular stripes diverging from the pylorus into the antrum <i>"Watermelon stomach"</i> Diffuse pattern of small reddish vascular spots observed in the antrum <i>"Honeycomb stomach"</i>	Combination of mosaic pattern of small reddish vascular spots, black – brown spots
Histological features		Superficial hyperplastic gastric antral mucosa, capillary ectasia with thrombosis and fibromuscular hyperplasia in the lamina propria, abnormal submucosal vasculature. Positive immunohistochemical markers: CD3, CD34, CD61	Submucosal vascular dilatation
Response to beta-blockers, transjugular intrahepatic shunt (TIPS) treatment		No response to treatment	Good response to treatment

slightly raised above the mucosal surface, cherry red in color, and 2–10 mm in size [47]. The syndrome appears in two distinct endoscopic forms: "watermelon stomach", characterized by longitudinal flat rows and reddish stripes diverging from the pylorus into the antrum, and "honeycomb stomach", described as diffuse pattern of small spots observed mainly in the antrum [48–50]. At endoscopic ultrasound examination, the gastric antrum appears hyperthrophic with a spongy appearance of the mucosa and submucosa and a well-preserved muscularis propria [51, 52].

In most cases, endoscopy findings are sufficient to diagnose GAVE syndrome, but there are important histological features which can be helpful. For instance, fibromuscular proliferation and capillary ectasia with microvascular thrombosis of the lamina propria, which form the histological hallmark of GAVE [12, 52]. Other histological features include hyperplastic gastric antral mucosa, fibrohyalinosis, and abnormal submucosal vasculature [54]. Westerhoff et al. described immunohistochemical staining for vascular markers CD31 and CD34, as well as the platelet maker CD61, to help highlight the increased mucosal microvessel density and microthrombi [55]. This investigation can help to distinguish GAVE syndrome from portal hypertensive gastropathy, when endoscopy does not show typical appearances of these conditions.

In 1989 Gilliam et al. proposed a score system to diagnose GAVE syndrome that was comprised of two histological criteria: the co-presence of ectasia and/or fibrin thrombi and spindle cell proliferation (Gilliam's score) [54]. A third parameter, fibrohyalino-

sis, was added to improve both sensitivity and specificity of diagnosis [33]. This "GAVE score" increased diagnostic accuracy to up to 80% in differentiating GAVE syndrome from portal hypertensive gastropathy.

DIFFERENTIAL DIAGNOSIS

Clinical dilemmas can arise when differentiating GAVE syndrome from other causes of upper gastrointestinal bleeding which mainly include portal hypertensive gastropathy (PHG) and hemorrhagic gastritis. In 1995 Payen et al. established that PHG and GAVE syndrome are distinct entities for the pathophysiological mechanisms and as such they require different treatments, therefore, it is vital to distinguish between them [33] (Table).

Endoscopically, GAVE syndrome is most commonly limited to the antrum, whereas PHG is predominantly involved in the fundus and corpus mucosa with characteristic endoscopic appearance [3]. Non-cirrhotic patients more frequently present the typical endoscopic "watermelon stomach" (striped pattern) that is more prevalent in middle-aged women, whereas the "honeycomb stomach" (diffuse pattern) typically appears in patients with liver failure [1, 32, 50]. The frequency of PHG in patients with portal hypertension has been reported to vary between 10% and 80% [56–59], and its treatment is mainly based on reducing portal pressure. The use of nonselective beta-blockers, particularly propranolol, has been studied in this setting and some studies showed that it induces a lower rate of hemorrhage, an increase in hemoglobin levels, and an improvement in the endoscopic appearance of the lesions [60]. Patients

not responding to beta-blockers should also be considered for TIPS, which has been shown to help with regression of endoscopic lesions by rapidly reducing portal pressure [61]. Yet other studies showed that GAVE syndrome does not respond to measures that decrease portal pressures in PHG and has no significant impact on its appearance [1, 10, 12, 19]. Biopsy has proved to be the best way of distinguishing between GAVE syndrome and portal hypertensive gastropathy [33]. Sometimes "watermelon stomach" can be wrongly interpreted as refractory hemorrhagic gastritis. In contrast to antral gastritis, lesions of GAVE are typically sharply demarcated with small marginated red spots, vessels blanch with pressure and bleed freely on endoscopic biopsy [62].

THERAPY

Therapies for GAVE aim to control the symptoms of acute or chronic blood loss, eliminate or reduce transfusion dependence, and improve patient's life quality. While there have been numerous non-invasive, endoscopic, and surgical therapy choices proposed over the past two decades, the best treatment option is yet to be defined.

Non-invasive therapy

Non-invasive therapy is usually aimed at diminishing the symptoms and used for the correction of the chronic or acute blood loss. It includes initial intravenous fluid therapy and blood product transfusions for acute bleeding episodes, as well as iron supplementation [12, 19].

Many medical therapies have been proposed over the years as a non-inva-

sive alternative for the treatment of GAVE related hemorrhage; however, none of them have shown satisfactory results in order to be considered a preferable alternative to invasive approaches [32]. Therapies such as estrogen-progesterone, corticosteroids, tranexamic acid, cyproheptadine and thalidomide have shown positive results in case reports and small clinical trials, but haven't shown sufficient efficacy to function as alternatives to endoscopic modalities [11, 23, 56–60, 64, 66–77]. Moreover, long term medical therapy can induce some severe side effects such as menorrhagia and gynecomastia, increase the risk of endometrial and breast cancer (after estrogen-progesterone therapy) [78], steroid-induced diabetes mellitus, cushing-like syndrome (after corticosteroids therapy) [11, 23, 64, 66–74], central venous stasis retinopathy, deep venous thrombosis, and pulmonary embolism (after tranexamic acid) [72–74]. Medical therapy aimed at reducing portal pressure had limited success in the treatment of GAVE syndrome [19]. Furthermore, the study reporting an improvement in bleeding from gastric mucosal lesions achieved by beta-blockers proved to be of little value as it did not distinguish between GAVE syndrome and portal hypertensive gastropathy which is well known to respond to a reduction in portal pressures by propranolol [79–80]. In a group of 8 patients with GAVE syndrome and cirrhosis, neither beta-blockade (nadolol) nor shunting of the portal venous system with a transjugular intrahepatic shunt (TIPS) led to control of chronic blood loss [20]. In conclusion, drug therapies have no definite role in the cure of GAVE-related bleeding and should be considered only as experimental therapeutic approaches in the setting of controlled clinical trials.

Argon plasma coagulation

In patients with active hemorrhage, endoscopic hemostatic therapy is generally the initial form of treatment. Argon plasma coagulation (APC) has been successfully used in the treatment of both the striped and diffused patterns of GAVE [50, 81] and is considered the preferred and the most frequently used endoscopic therapy method. APC is a noncontact electrocoagulation technique that uses a jet of ionized argon gas to deliver monopolar high-frequency current to the target tissues; it successfully reduces bleeding by obliterating the ectatic vasculature [32, 82]. The benefits of

APC lies in the consideration that the depth of penetration can be easily controlled (0.5–3 mm) thus avoiding excessive blood loss [32, 83, 84]. Multiple sessions may be required to reduce future episodes and/or decrease transfusion dependence, and repeated endoscopic therapy improves the probability of cure. The number of sessions needed to eradicate GAVE depends on the pattern, the extent and the number of lesions. Intervals of 4 to 6 weeks between sessions are recommended to ensure complete healing from previous treatment [23, 85]. Nakamura et al. showed that the recurrence-free rate and survival rate after APC declined over time. Cumulative recurrence-free rates were 49.7% after 1 year, 35.5% after 2 years, and 35.5% after 3 years with post-treatment survival rates of 94.4%, 75.8%, and 64.9% at 1, 2, and 3 years respectively [86]. However, APC has a higher risk of sepsis, antral stenosis, and gastric outlet obstruction, as well as other post-procedure complications [87, 88].

Radiofrequency ablation

Radiofrequency Ablation (RFA) is a minimally invasive procedure that uses short (less than 1 s) high-energy (11–20 J) pulses to ablate the superficial mucosal lesions of the muscularis mucosa, resulting in less damage to the submucosal layer [89]. Some studies demonstrate successful use of this modality in patients with lower gastrointestinal bleeding from ectatic vessels to secondary chronic radiation proctitis, including those patients refractory to other treatment modalities [90]. The patients responded to RFA procedures favorably with improved hemoglobin levels and a decrease in transfusion requirement with no significant complications [90]. The results are promising for the future of RFA in the treatment of GAVE syndrome.

Band ligation

Endoscopic band ligation (EBL) has been proven to be a safe and effective treatment of GAVE syndrome [91–96]. This technique has been used as the standard treatment in other gastrointestinal (GI) vascular disorders, such as esophageal varices or hemorrhoids, and tends to be a safer option than its surgical/thermoablative counterparts, which makes it a viable option for the treatment of GAVE syndrome as well. Recently, Wells et al. [95] reported a study demonstrating the superiority of endoscopic band ligation in the treatment of GAVE, when compared

to endoscopic thermal therapy. It was found that early band ligation had a significantly higher rate of bleeding cessation, fewer treatment sessions were required to achieve bleeding cessation, it caused a greater increase in hemoglobin levels, a greater decrease in transfusion requirements, and a greater decrease in hospital admissions during the follow-up period [96]. No randomized, prospective studies have been carried out to conclusively demonstrate the superiority of endoscopic band ligation over conventional therapies, but it offers a promising new therapeutic option.

YAG laser coagulation

Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser technology, which produces rapid thermal destruction of tissue, has been widely used in the treatment of GAVE syndrome [12, 97]. Nd:YAG lasers exhibit deeper mucosal injury to a depth of 4–6 mm, allowing coagulation of superficial and submucosal vessels without direct contact. In one study, 13 transfusion-dependent patients were treated with a Nd:YAG laser. A few of them showed remarkable response with a complete elimination of transfusion requirement over a median follow-up of two years [23]. The main disadvantage of this method is its higher cost, making other treatment modalities with similar efficacy more attractive.

Surgical antrectomy

Before the advent of endoscopic therapy, GAVE syndrome was commonly treated by surgical antrectomy [6, 11, 12]. Nowadays this treatment can be considered for patients with more extensive vascular malformations that are refractory to medical or endoscopic therapies [98]. Novitsky et al. found surgical gastric resection as the only reliable therapy with definitive and curative potential which can eliminate the bleeding, anemia and red blood cell transfusion dependence in failure of endoscopic therapy and recurrent episodes of gastrointestinal bleeding [12]. Even though surgical antrectomy provides the most complete therapy for GAVE syndrome, this method has significant mortality and morbidity risks, especially in the presence of portal hypertension or liver cirrhosis, owing to increased bleeding risk from abdominal collateral vessels in the setting of severe portal hypertension [20]. Portacaval shunts for reduction of portal hypertension (including TIPS) do not affect the bleeding and have no

role in the treatment of GAVE syndrome [20]. It has been reported that orthoptic liver transplantation can improve overall patient's condition and lead to a complete resolution of this disease [4].

DISCUSSION

Although GAVE syndrome is involved in only 4 % of non-variceal upper gastrointestinal bleeding developments [1], it may have serious and severe consequences. The diagnosis of this syndrome is problematic because it can be overshadowed by other frequent bleeding causes like peptic ulcer disease, gastric mucosal erosions, Mallory-Weiss syndrome, gastrointestinal cancer, and other reasons [2]. Typical initial presentations of the syndrome range from occult bleeding causing transfusion-dependent chronic iron-deficiency anemia to se-

vere acute upper gastrointestinal bleeding [19]. The way to suspect and anticipate the occurrence of this syndrome is to know what disorders it may coexist with. In literature, conditions such as liver cirrhosis, autoimmune connective tissue disorder, bone marrow transplantation, ischemic heart disease, valvular heart disease, hypertension, hypothyroidism, diabetes, and acute myeloid leukemia [3–8] are associated with the appearance of gastric ectasia. Recently, more and more case reports describe ESRD with a high incidence of GAVE syndrome [9]. It has been suggested that impaired renal excretory function and decreased removal of vasoactive substances from the circulatory system may be associated with the emergence of gastric vascular ectasia [23–28]. The initial form of treatment was APC [50, 81], which is considered the preferred and the most frequently used method of endoscopic therapy.

CONCLUSIONS

In conclusion, GAVE syndrome is an important cause of upper gastrointestinal bleeding and has a higher prevalence in patients with renal insufficiency. Realization of the etiology and characteristics are essential for doctors to suspect, diagnose, and treat gastric ectasia in patients, especially in those with more than one risk factor and showing signs of treatment refractory anemia. Only proper diagnosis and well-timed disease treatment can significantly improve patient's medical condition and future prognosis.

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Santrauka

SKRANDŽIO URVO KRAUJAGYSLIŲ EKTAZIJA SERGANT LĖTINE INKSTŲ LIGA: LITERATŪROS APŽVALGA

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Įvadas. Skrandžio urvo kraujagyslių ektazija yra viena pavojingiausių viršutinės virškinimo trakto dalies kraujavimo priežasčių. Ji sukelia iki 4 % visų nevarikozinės kilmės kraujavimų. Ši patologija tipiška pasireiškia vidutinio amžiaus moterims ir yra vis dažniau aptinkama inkstų nepakankamumu ar lėtine inkstų liga sergantiems pacientams. Skrandžio urvo kraujagyslių ektazija, kitaip vadinama „arbūzinių pilvu“, yra diagnozuojama remiantis gastroduodenoskopijos vaizdais,

būdingu pogleivio kraujagyslių išsiplėtimu, besitiesiančiu palei išilgines skrandžio gleivinės raukšles ir dažniausiai išsidėsčiusiu prievarčio urvo sityje. Nors ligos patogenezė nėra iki galo aiški, literatūroje pateikiamos mechaninio streso, humoralinių ir autoimuninių veiksnių teorijos. Per pastaruosius du dešimtmečius buvo siūlytos chirurginės intervencijos, endoskopinės procedūros ir farmakologinė terapija, siekiant rasti efektyviausią skrandžio urvo ektazijos gydymą. Nors jis ir iki šios dienos lieka išsū-

kiu, argono plazmos koaguliacija yra pripažinta efektyviausiu gydymo metodu.

Apibendrinimas. Skrandžio urvo kraujagyslių ektazija pripažinta pavojinga būkle, kuri pasitaiko inkstų nepakankamumu ir lėtine inkstų liga sergantiems pacientams. Didžiausios kraujavimo rizikos grupei yra priskiriami pacientai, kurie turi gydymui atsparios anemijos rodiklius. Klinikistams būtina žinoti sindromo etiologiją ir klinikinę charakteristiką, kad gebėtų įtarti, diagnozuoti ir gydyti šią būklę. Tik kryptinga sindromo diagnostika ir nepavėluotas gydymas užtikrina paciento būklės stabilumą ir geresnę ligos prognozę.

Reikšminiai žodžiai: skrandžio urvo kraujagyslių ektazija, „arbūzinis pilvas“, inkstų nepakankamumas, lėtinė inkstų liga, hemodializės komplikacijos.

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