

Diagnosis and management of gastric antral vascular ectasia

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sclerodactyly, are co-present in about 60% of patients with GAVE; other autoimmune and connective tissue disorders are occasionally reported such as Sjogren's syndrome, systemic lupus erythematosus, primary biliary cirrhosis and systemic sclerosis. In the remaining cases, GAVE syndrome has been described in patients with chronic renal failure, bone marrow transplantation and cardiac diseases. The pathogenesis of GAVE is still obscure and many hypotheses have been proposed such as mechanical stress, humoral and autoimmune factors and hemodynamic alterations. In the last two decades, many therapeutic options have been proposed including surgical, endoscopic and medical choices. Medical therapy has not clearly shown satisfactory results and surgery should only be considered for refractory severe cases, since this approach has significant mortality and morbidity risks, especially in the setting of portal hypertension and liver cirrhosis. Endoscopic therapy, particularly treatment with Argon Plasma Coagulation, has shown to be as effective and also safer than surgery, and should be considered the first-line treatment for patients with GAVE-related bleeding.

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Key words: Gastric antral vascular ectasia; Bleeding; Watermelon stomach; Argon plasma coagulation

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Abstract

Gastric antral vascular ectasia (GAVE) is an uncommon but often severe cause of upper gastrointestinal (GI) bleeding, responsible of about 4% of non-variceal upper GI haemorrhage. The diagnosis is mainly based on endoscopic pattern and, for uncertain cases, on histology. GAVE is characterized by a pathognomonic endoscopic pattern, mainly represented by red spots either organized in stripes radially departing from pylorus, defined as watermelon stomach, or arranged in a diffused-way, the so called honeycomb stomach. The histological pattern, although not pathognomonic, is characterized by four alterations: vascular ectasia of mucosal capillaries, focal thrombosis, spindle cell proliferation and fibrohyalinosis, which consist of homogeneous substance around the ectatic capillaries of the lamina propria. The main differential diagnosis is with Portal Hypertensive Gastropathy, that can frequently co-exists, since about 30% of patients with GAVE co-present a liver cirrhosis. Autoimmune disorders, mainly represented by Reynaud's phenomenon and

INTRODUCTION

Gastric antral vascular ectasia (GAVE) is an uncommon but often severe cause of upper gastrointestinal (GI) bleeding, responsible of about 4% of non-variceal up-

per GI hemorrhage^[1]. This disease was first described in 1953 by Ryder *et al*^[2], but deeply investigated only 25 years later, in 1978, by Van Vliet *et al*^[3]. Since then, a better but still incomplete knowledge of this condition has been reached; however, the exact prevalence is not known, the pathogenesis remains unclear and the best therapeutic approach has not yet been defined. The aim of this paper is to review the current findings about GAVE and to contribute to a better understanding of this often misdiagnosed disease and critically review the current therapeutic options.

MORPHOLOGICAL ASPECTS

GAVE is characterized by a pathognomonic endoscopic pattern, mainly represented by red spots either organized in stripes radially departing from pylorus, defined as watermelon stomach, or arranged in a diffused way, the so called honeycomb stomach^[4] (Figures 1 and 2).

GAVE is typically located in the gastric antrum, however it may be rarely found also in other areas of the GI tract, including cardia^[5,6], duodenum, jejunum^[7] and rectum^[8,9]. The involvement of the proximal part of the stomach is almost rare and generally located within a diaphragmatic hernia^[10]. At the endoscopic ultrasound (EUS), the gastric antrum appears hypertrophic with a spongy appearance of the mucosa and submucosa and a well-preserved muscularis propria^[11,12].

The histological pattern, although not pathognomonic, is characterized by four alterations: vascular ectasia of mucosal capillaries, focal thrombosis, spindle cell proliferation (= smooth muscle cell and myofibroblast hyperplasia) and fibrohyalinosis, which consist of homogeneous substance around the ectatic capillaries of the lamina propria^[13-15] (Figures 3 and 4). In 1989, Gilliam *et al*^[14] proposed a score system to diagnose GAVE, which considered only two histological criteria: the co-presence of ectasia and/or fibrin thrombi and spindle cell proliferation (Gilliam's score). Subsequently, a third parameter, fibrohyalinosis, was added to improve both sensibility and specificity^[15]. This latter score, called "GAVE score", showed a higher diagnostic accuracy (80%) to differentiate GAVE from Portal Hypertensive Gastropathy, which may be present in patients with co-existing portal hypertension. Table 1 summarized both the histological scores, the Gilliam's score and the GAVE score.

GAVE VS PORTAL HYPERTENSIVE GASTROPATHY: DIFFERENTIAL DIAGNOSIS

Patients with portal hypertension often present an endoscopic pattern called portal hypertensive gastropathy (PHG), which needs to be distinct from the GAVE pattern, since they represent two separate entities in the setting of liver cirrhosis. The differential diagnosis is mainly based on the endoscopic appearance and, in the doubtful



Figure 1 Endoscopic appearance of gastric antral vascular ectasia: Red spots radially departing from pylorus and involving the gastric antrum.



Figure 2 Videocapsule image of gastric antral vascular ectasia.

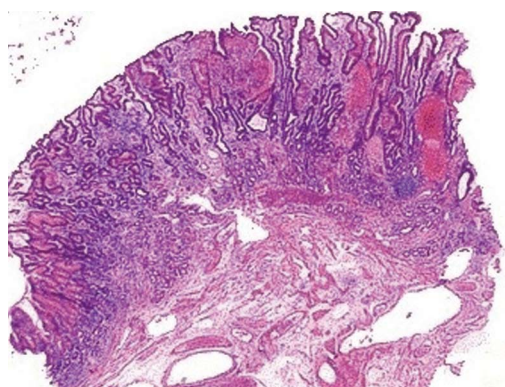


Figure 3 Gastric biopsy showing prominent vascular congestion with thrombosis of the vasculature. The surrounding glands appear regenerative and the vessels in the submucosa are dilated and sclerotic.

cases, by the histological pattern.

PHG occurs only in patients with portal hypertension and typically involves the fundus and the corpus of the stomach; the endoscopic pattern is characterized by a combination of four main characteristics: a mosaic-like pattern, presence of red point lesions, cherry red spots and black-brown spots^[16]. The histological findings may clarify the uncertain cases by the assessment of the "GAVE score", indeed, a GAVE score > 3 is considered highly diagnostic for the presence of GAVE (Table 1)^[15].

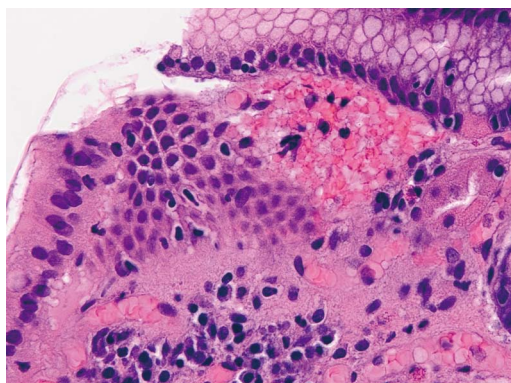


Figure 4 Higher magnification of one of the thrombosed vessels.

Table 1 Histological score systems for diagnosis of gastric antral vascular ectasia

Gastric antral vascular ectasia score (range 0-5)			Gilliam's score (range 0-4)
Score	Fibrin thrombi and/or vascular ectasia	Spindle cell proliferation	Fibrohyalinosis
0	Both absent	Absent	Absent
1	One present	Increased	Present
2	Both present	Marked increased	-

The main aspects to consider in the differential diagnosis between GAVE and PHG are summarised in Table 2. The importance to distinguish these two clinical entities is mainly related to the different therapeutic approach; the reduction of portal pressure by using drugs (beta-blockers, somatostatin, octreotide), trans-jugular intra-hepatic porto-systemic shunt (TIPS) or surgery (portocaval shunts) are not effective for the treatment of GAVE^[17,18].

GAVE AND ASSOCIATED DISEASES

GAVE syndrome can complicate the course of many diseases (Table 3). Autoimmune disorders, mainly represented by Reynaud's phenomenon and sclerodactyly, are co-present in about 60% of patients with GAVE^[10]; other autoimmune and connective tissue disorders are occasionally reported such as Sjogren's syndrome^[19], systemic lupus erythematosus^[20], primary biliary cirrhosis and systemic sclerosis^[21]. In this latter case, it has been reported that GAVE can even represent the presenting syndrome, preceding the development of the autoimmune disorders by several months^[21].

About 30% of patients with GAVE co-present a liver cirrhosis^[22-24], whatever etiology (viral, autoimmune, toxic-metabolic). In the remaining cases, GAVE syndrome has been described in patients with chronic renal failure^[10], bone marrow transplantation^[25] and cardiac diseases^[10,26].

Non-cirrhotic patients more frequently present the typical endoscopic watermelon-, striped-pattern and are mainly represented by middle-aged women whereas the honeycomb-, diffuse-pattern prevails in patients with liver failure^[1,4,27]. However, the endoscopic appearance is

Table 2 Differential diagnosis between portal hypertensive gastropathy and gastric antral vascular ectasia

Features	Portal hypertensive gastropathy	Gastric antral vascular ectasia
Site	Fundus-corpus	Antrum
Endoscopic pattern	Combination of: Mosaic-like pattern Red point lesions Cherry red spots Black-brown spots	Red spots organised: Striped-pattern (watermelon-stomach) Diffused-pattern (honeycomb-stomach)
Histological pattern	Not specific	Highly specific
Response to β -Blockers/transjugular intrahepatic portosystemic shunt/portocaval shunts	Present	Absent

Table 3 Gastric antral vascular ectasia and associated diseases

Associated disease	Prevalence (%)	Ref.
Autoimmune diseases	60	
Raynaud's phenomenon		[10]
Sclerodactyly		[10]
Sjogren's syndrome		[19]
Systemic sclerosis		[21,32]
Primary biliary cirrhosis		[10,32]
Systemic lupus erythematosus		[20]
Liver cirrhosis and/or portal hypertension	30	[22-24]
Others	10	
Chronic renal failure		[10]
Bone marrow transplantation		[25]
Cardiac diseases		[10,26]

not related to the patient's outcome^[4] but could reflect a different pathogenesis.

PATHOGENESIS

GAVE syndrome is an acquired disease rather than a congenital alteration. The pathogenesis of GAVE is still obscure and many hypotheses have been proposed such as mechanical stress, humoral and autoimmune factors and hemodynamic alterations.

Mechanical stress represented by strong gastric peristalsis has been supposed to induce prolapse and trauma of antral mucosa and intermittent obstruction of blood vessels, which can lead to fibro-muscular hyperplasia and vascular ectasia^[28]. These latter are typical findings of GAVE and other gastrointestinal lesions due to repeated traumas and mucosal prolapse (i.e., stomas and prolapsed haemorrhoids)^[13]. Furthermore, a subset of patients with liver cirrhosis and GAVE has been shown to have antropyloric dysfunction with abnormal antral motor response to meals^[29].

Many authors have assumed a pivotal role of humoral factors as gastrin, vasoactive inhibitory peptide (VIP), 5-hydroxytryptamine, glucagon, catecholamines, prostanoïd and other undefined vasoactive substances. GAVE syndrome has been associated with both increased^[28] and decreased levels of gastrinemia^[15] and these conflicting data reduced the importance initially ascribed to this

hormone, which was hypothesised to induce spindle cell proliferation, hyperplasia, prolonged sphincter relaxation and also capillary and venous dilatation. A possible role of both VIP and 5-hydroxytryptamine has been proposed after the evidence of the presence of actively proliferating neuroendocrine cells surrounding the ectatic vessels in the lamina propria of patients with GAVE^[30]. The release of these substances seems to be responsible for the local vasodilatation and the tendency to bleed. On the other hand, glucagon and catecholamines do not seem to play any role in the pathogenesis of GAVE, since concentrations of these metabolites have shown to be similar in cirrhotics with or without GAVE. However, prostaglandin E₂, a prostanoid with vaso-dilatator and acid-inhibitory effect, showed significantly higher levels in patients with GAVE^[31].

Up to 60% of patients with GAVE have also an autoimmune associated disease and show the presence of autoantibodies^[10], therefore an autoimmune pathogenesis has been suggested. Indeed, several autoantibodies have been detected in patients with GAVE; Watson *et al*^[32] found that all patients with systemic sclerosis and GAVE were positive for antinuclear antibodies and, in some cases, were also positive for anti-centromere antibodies. This antibody was subsequently demonstrated to recognize a specific and formerly unknown centromeric protein, involved in the cell growth process^[33]. Garcia *et al*^[34] and Valdez *et al*^[35] found in the sera of a patients with GAVE an antinucleolar antibody that specifically recognized a RNA helicase II (RH-II). It has been speculated that these autoantibodies could cross-react with specific proteins present in the vessels of the gastric mucosa and sub-mucosa inducing the typical alterations. However, the exact role played by these autoantibodies is still unknown and only the development of an animal model will probably provide further information.

It is now evident that portal hypertension does not play a role in the GAVE development, since it is not present in up to 70% of patients, and the reduction of portal hypertension does not affect the course of the disease^[17]. Moreover, it has been shown that liver transplantation despite persistent portal hypertension induces complete disappearance of the antral vascular lesions^[36]. It could be speculated that liver failure, at least in a subset of patients, and not portal hypertension, could have a role in the pathogenesis of GAVE altering the metabolism of not yet identified substances.

Finally, GAVE syndrome could have a multifactorial pathogenesis, with the driven process strictly related to the different clinical settings (i.e., autoimmune or liver failure setting), thus explaining the dissimilar endoscopic appearance (watermelon- or honeycomb-pattern).

THERAPEUTIC OPTIONS

In the last two decades, many therapeutic options have been proposed including surgical, endoscopic and medical choices and the best approach is still to be defined.

Surgery

The surgical approach, most commonly represented by antrectomy, has a clear clinical efficacy in the management of GAVE-related bleeding, since none of the patients surgically treated has recurrence of bleeding in the post-operative period^[37]. However, this approach has significant mortality and morbidity risks, especially in the setting of portal hypertension and liver cirrhosis. Novitsky *et al*^[37] reviewed 45 reported surgical cases and found that antrectomy was the most frequently performed surgical approach (89% of cases) with a 30-d mortality rate of 6.6% and the principal cause of death was multiorgan failure. As previously mentioned, portocaval shunts, including TIPS, have no role in the treatment of GAVE syndrome^[17].

Medical therapy

A wide variety of drugs have been used to try to control GAVE-related bleeding, however no one has clearly shown satisfactory results in order to consider medical therapy as a valid alternative to an invasive approach.

Hormonal therapy - estrogen-progesterone - has been shown to control bleeding related to GI vascular malformations, including GAVE, by undefined mechanisms^[38,39]. However, since the vascular lesions persist despite cessation of bleeding, a dose-reduction is usually related to bleeding relapse^[40-42]. Moreover, the long-term treatment with hormonal-therapy can induce severe side effects, such as menorrhagia and gynaecomastia, and increase the risk of endometrial and breast cancer^[43].

Ocreotide, a long-acting somatostatin analogue, has been shown to effectively control chronic bleeding related to vascular abnormalities. Nardone and co-workers treated 3 patients with GAVE-related bleeding with ocreotide (0.1 mg subcutaneous three times a day) for 6 mo, obtaining a transient reduction of bleeding in one case and cessation in the others two patients, with partial and total regression of the lesions^[44]. This result can be partly explained by several effects exerted by this hormone such as the inhibitory effect on both neuroendocrine cells surrounding the ectatic vessels and on smooth muscle cells, and the anti-angiogenic effect. However, other authors have not confirmed these results^[45] and the role played by ocreotide needs to be further investigated in larger sample size studies.

Few case-reports have suggested a potential benefit from the use of tranexamic acid but reported severe side effects (central venous stasis retinopathy; deep venous thrombosis and pulmonary embolism) limit its use^[46-48].

A case-report showed complete resolution of GAVE with intravenous infusion of methylprednisolone and cyclophosphamide in a patient with associated systemic sclerosis and pernicious anaemia^[49]; but, such result has not been yet confirmed in larger series.

In conclusion, drug therapies have no definite role in the cure of GAVE-related bleeding and should be considered an experimental therapeutic approach in the setting of controlled clinical trials.



Figure 5 Argon plasma coagulation treatment of gastric antral vascular ectasia in patient with transfusion-dependent anaemia.

Endoscopic treatment

The endoscopic treatment principally represented by laser photoablation and, more recently, by Argon Plasma Coagulation (APC) has shown a similar and safer effect as surgery.

Neodymium-yttrium-aluminum garnet (Nd: YAG) laser coagulation has been successfully used to control GAVE-related bleeding. All series have confirmed the efficacy of this endoscopic thermal therapy by reducing or abolishing the need of blood transfusions in about 50% to 80% of cases, with a mean of 3 treatment sessions (range 1-10)^[50-53].

The most serious complication described after laser therapy, even if rare, is represented by gastric perforation. Two weeks after almost all laser therapy sessions, a gastric ulceration is frequently observed, even when the laser treatment session has been performed with an energy power sufficient to induce only superficial scarring without deep tissue necrosis^[54]. Another complication observed after repeated treatment sessions, is pyloric stenosis, that can induce either delayed gastric emptying or true obstruction^[54,55]. Up to 8% of patients developed this complication, that can be resolved by balloon dilation^[55]. Moreover, after multiple, high energy, laser therapy sessions, patients may develop hyperplastic polyps, even after 20 mo of follow-up^[56]. These polyps can reach large dimensions and induce recurrent anaemia without evidence of recurrence of vascular abnormalities^[56]. Their development is thought to be secondary to reactive foveolar hyperplasia and no focal malignancy has been detected. However, Bernstein and co-workers presented a case-report of a multifocal gastric cancer developed after repeated sessions of laser therapy over a five-year period^[57].

Other important disadvantages of laser endoscopic therapy are the high cost and the need of a long training period, since most severe complications, such as perforation and death, happen more frequently when the endoscopist is not sufficiently skilled with the procedure^[51,54].

Argon plasma coagulation (APC) is a noncontact technique with a controllable depth of coagulation (0.5-3 mm). High-frequency current is applied to the tissue

through ionized and electrically conductive gas, called argon plasma; the diverging gas flow allows an axial, radial and retrograde application (Figure 5). In comparison to Nd: YAG laser therapy, APC is easier to use, more manageable, cheaper and, most importantly, safer; nevertheless, randomized trials comparing the two endoscopic procedures are lacking.

The complications are rare and mostly mild. The most frequently reported complication is represented by intestinal gas distension related to argon flow, which can leave the patient with a feeling of discomfort after the endoscopic session. Wall emphysema and intestinal pneumatosis have been described, but these conditions are usually reversible^[58]. More serious adverse events described after APC treatment are asymptomatic antral stenosis^[59] and upper GI hemorrhage. One severe case of sepsis, which conducted to death due to infectious peritonitis, has also been described^[60]. The risk of intestinal perforation is very low and limited to very thin-walled structures (i.e., caecum)^[58,61]; notably, no case of perforation during APC treatment of GAVE has been described.

The largest case series of APC treatment reported an efficacy ranging from 90%^[60] to 100%^[62], with no further need for blood transfusions and an increase of hemoglobin level from 2.3 g/dL^[62] to 5.5 g/dL^[58] in almost all patients. The setting of argon gas flow usually ranges between 0.8 L/min and 2.5 L/min, the electrical power from 40 W to 100 W and, generally, a mean of 2.5 sessions are needed to achieve complete eradication^[58,62,63].

Several other endoscopic therapies have been proposed in the last years, such as cryotherapy, band ligation and radiofrequency ablation.

A small, prospective pilot study, based on 12 patients, investigated the efficacy of cryotherapy for the treatment of GAVE-related bleeding achieving a complete response to treatment (i.e., no need for blood transfusion) in 50% of cases^[64]. Cryotherapy is based on the rapid decrease of temperature due to the rapid expansion of carbon dioxide (CO₂) released by the spray catheter; such sudden decrease of temperature causes superficial necrosis of the mucosa and of the superficial submucosal, with eradication of antral teleangiectasias, and subsequent re-epithelialization. The need for specialized equipment and for specific training, represents Cryotherapy's main limitations; furthermore, the need of an overtube placed to enable passive venting of CO₂, might add technical difficulty and risk to the procedure.

Several case-reports and one observational comparative study have reported the use of band ligation for patients with GAVE related bleeding^[65-67]. Based on the small, retrospective study that compared endoscopic band ligation with endoscopic thermal therapy, band ligation showed a significant higher rate of bleeding cessation, fewer treatment sessions required to achieve cessation of bleeding, a greater increase in hemoglobin values and reduction of the need for transfusions^[67]. The higher efficacy compared to standard thermal therapy is probably due to a more reliable eradication of the abnormal

vasculature in the mucosa and submucosal.

Finally, a pilot study has investigated the role of radiofrequency ablation for the treatment of GAVE^[68]; 6 patients with transfusion-dependent GAVE-related bleeding were enrolled and after 1 to 3 treatments, all but one no longer needed transfusions during the 6 mo follow up, without reporting adverse events.

Although cryotherapy, endoscopic band ligation and radiofrequency ablation have provided encouraging results, well-performed, larger, prospective studies are needed before providing any definitive conclusion.

CONCLUSION

GAVE is an infrequent but severe cause of upper gastrointestinal bleeding, characterized by a pathognomonic endoscopic pattern of red spots organized either in stripes or randomly distributed in the gastric antrum. GAVE can develop in the setting of many diseases, mainly represented by autoimmune diseases and liver cirrhosis. Although many hypotheses, such as mechanical stress, humoral/immunological factors and haemodynamics alterations, have been proposed, the pathogenesis of GAVE remains still obscure and probably different pathways occur in different clinical settings. The therapy is limited to surgical or endoscopic approach, since most drug therapies have shown conflicting results. Surgery has the advantage to be a definitive therapy but with high morbidity and mortality risks, especially in patients with severe co-morbidities, such as liver cirrhosis. Endoscopic therapy, particularly treatment with APC, has shown to be as effective and also a safer than surgery, and should be considered the first-line treatment for patients with GAVE-related bleeding.

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