Argon plasma coagulation in the management of symptomatic gastrointestinal angiodysplasia: experience in 69 consecutive patients

Traitement des angiodysplasies digestives hémorragiques par éléctrocoagulation au plasma argon : à propos de 69 cas

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RÉSUMÉ

Prérequis: Les angiodysplasies gastro-intestinales représentent la principale cause de saignement gastro-intestinal occulte. But : Evaluer l'efficacité de l'électrocoagulation au plasma argon dans le traitement des angiodysplasies gastro-intestinales hémorragiques et identifier les facteurs prédictifs de succès de cette technique.

Méthodes: Il s'agit d'une étude rétrospective incluant des patients ayant des lésions d'angiodysplasies gastro-intestinales hémorragiques traitées par électrocoagulation au plasma argon dans le service de gastro-entérologie de l'hôpital militaire de Tunis entre Janvier 2000 et Décembre 2011. L'efficacité de la technique d'hémostase a été jugée sur les besoins transfusionnels, le taux d'hémoglobine avant et après APC et la récidive hemorragique.

Résultats: Soixante-neuf patients d'âge moyen de 68,7 ans ont été inclus. Le traitement endoscopique a permis une ascension du taux d'hémoglobine de 7,3 à 9,3g/dl (p=0,0001) et la diminution des besoins transfusionnels de 2,5 à 0,1 culots globulaires (p<0,0001). Il a également permis d'éviter la chirurgie chez 93,6% des patients ayant des antécédents chargés. Une récidive hémorragique a été observée chez 33,3% des patients après une moyenne de 12,3 mois. En analyse multivariée, aucun facteur n'était indépendamment associé à la récidive hémorragique. La survie globale sans récidive hémorragique à 1 an et 2 ans étaient respectivement de 50% et 42%.

Conclusion: L'électrocoagulation au plasma argon est une technique d'hémostase simple, efficace et sans danger dans le traitement des angiodysplasies hémorragiques. Cette technique est particulièrement intéressante chez les patients ayant des antécédents chargés chez qui un traitement chirurgical serait grevé d'une importante morbi-mortalité.

Mots-clés

Angiodysplasies, Hémorragie digestive, Thérapeutique, Plasma argon

SUMMARY

Background: Gastrointestinal angiodysplasias are associated with a high bleeding risk. Aim: to evaluate the efficiency of argon plasma electrocoagulation in the treatment of gastrointestinal angiodysplasia and to identify predictive factors of success of this technique.

Methods: Retrospective study of patients with bleeding gastrointestinal angiodysplasia treated with argon plasma electrocoagulation in the digestive endoscopy unit of the military hospital in Tunis between January 2000 and December 2011.

Results: 69 patients with a mean age of 68.7 years were included. The endoscopic treatment resulted in a rise in hemoglobin value from 7.3 to 9.3 g/ dl (p = 0.0001) and a decrease of transfusion requirements from 2.5 to 0.1 units of packed red cells (p <0.0001). It allowed to avoid surgery for 93.6% of patients with complex medical history. Recurrence of bleeding was observed in 33.3% of patients after a mean time of 12.3 months. In a multivariate analysis, no factors were independently associated with the recurrence of bleeding. The overall survival without rebleeding at 1 and 2 years were 50% and 42% respectively.

Conclusion: Argon plasma coagulation is an easy, effective and safe treatment of bleeding angiodysplasia. This technique is particularly interesting for patients with multiple medical problems, where surgical treatment could be burdened by significant morbidity and mortality risk.

Key-words

Angiodysplasia, gastrointestinal bleeding, treatment, endoscopy, argon plasma coagulation

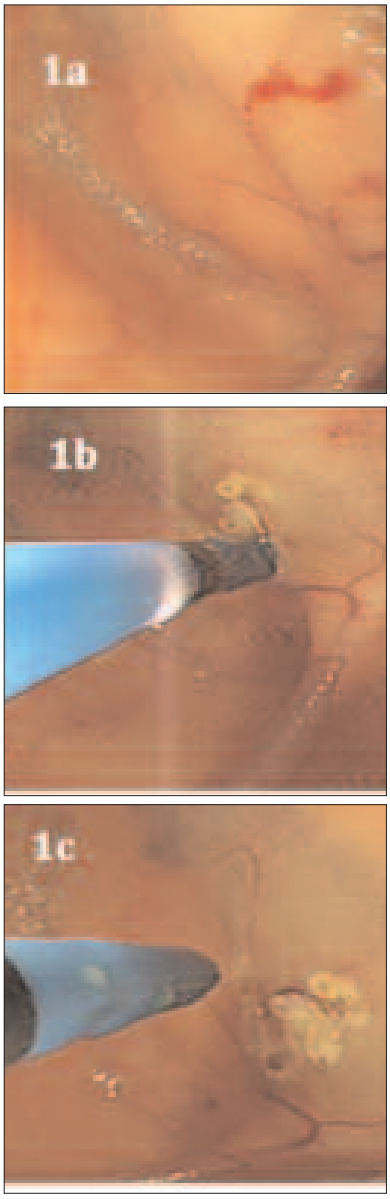
Many therapeutic approaches (medication, endoscopy and surgery) have been proposed to treat digestive angiodysplasias, but their effectiveness is controversial(1).
Endoscopic treatment is indicated as a first-line treatment. It is mainly based on argon plasma coagulation (APC). This hemostatic technique is increasing in popularity, and has to be evaluated. The aim of our study was to assess the efficacy and safety of argon plasma electrocoagulation in the treatment of gastrointestinal angiodysplasia in 69 patients and identify predictive factors of success of this treatment.

METHODS

We performed a retrospective analysis of 69 patients with digestive angiodysplasia treated by APC at the digestive endoscopy unit of the military hospital of Tunis between January 2000 and December 2011. Demographic data, including comorbidities and use of antiplatelet and anticoagulant agents, were collected at the time of the index procedure. We collected endoscopic findings and treatment details. All serious acute, early and late complications associated with APC therapy like perforation, submucosal emphysema, fever/infection, bleeding and stricture were documented. Follow-up information was collected by telephone interview with patients, who were asked about bleeding recurrence, the presence of anemia and their last hemoglobin level. Follow-up blood tests were obtained for all patients at least 3 months after initial treatment and at any stage during follow-up, if symptoms recurred. Patients with no recent hemoglobin level were invited to perform a blood count. All patients were explored by upper endoscopy and/or colonoscopy and, if no cause of bleeding was found, a videocapsule was performed. Single-channel endoscopes were used (Olympus GIF 180 and GIF CF-Q 240 L, Olympus Corporation, Tokyo, Japan). Standard APC equipment consisting of a high frequency generator (ICC 200), an automatically regulated argon source (APC 300) and a flexible reusable APC probe (2.3 mm in diameter, 220 cm, axial or lateral opening for the plasma beam) ERBE, electromedizin, Tuebingen, Germany. Colon preparation was done with polyethylene glycol according to the standard protocol of the department. Argon gas flow was set at 1.2 L/min. Electrical power was respectively set at 40 W for right colon, duodenal and small bowel lesions and 50–60 W for stomach, transverse and left colon and rectum. All lesions were treated until the mucosa became white in appearance after electrocoagulation. Each endoscopic session with APC lasted less than 30 minutes. Sessions were repeated until full eradication of the lesions. Patients were monitored during 6 hours after endoscopic treatment.
The following operative definition of angiodysplasia was applied: endoscopic finding of simple or multiple 2-mm to 5-mm flat bright red spots, with round uniform or slightly irregular margins, or lesions appearing as raised and reddened areas with a distinctly irregular margin >5 mm (fig 1). Bleeding presentation was defined according to two clinical forms: 1) occult bleeding, considered as the initial presentation of iron-deficiency anemia (hemoglobin level < 13.5 g/dl in males and < 12 g/dl in females), with no evidence of passing blood visible to the patient or physician; and 2) overt bleeding, considered as ongoing or previous fecal passage of visible blood (melena or hematochezia).

The bleeding recurrence was defined by the occurrence of a new episode of gastrointestinal bleeding or drop in hemoglobin >2g/dl after endoscopic treatment.

Figure 1: 1a : Caecal angiodysplasia; 1b : Argon plasma electrocoagulation of the angiodysplasia; 1c : Appearence of the lesion after argon plasma electrocoagulation



Statistical analysis:
Continuous variables are expressed as mean and standard deviation (SD). Categorical variables are expressed as totals and percentages and were analyzed using the chi-square test or Fisher's exact test. Univariate and multivariate logistic regression were used to analyze the factors related to recurrent bleeding after APC treatment.

A p value less than 0.05 was considered statistically significant. Free reccurence survival was studied using the Kaplan-Meier method. All statistical analysis were performed using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

1/ Demographics:

Sixty-nine patients were treated with APC for GI angiodysplasia (sex ratio 1.76 and mean age 68.7 years; range [21 – 87 yr]). A significant proportion had comorbidities (n=47: ischemic heart disease (n=16), chronic renal failure (n=14), valvular disease (n=4), cirrhosis (n=6), and diabetes (n=21)) and 26 patients were taking either anti-coagulant (n=13) or antiplatelet (n=16) therapy at the time of APC treatment. Clinical characteristics, blood test data and coexisting diseases are resumed in table 1.

Table 1: Clinical characteristics, blood-test data, and co-existing diseases in patients with angiodysplasia

Clinical characteristics		
Age (years) [mean +/- SD]	**70 +/- 12.3**	
Sex (sex ratio, M/F)	**1.76 [M/F = 44/25]**	
Coexisting diseases	**(n)**	**(%)**
Diabetes (n and %)	21	30
Cirrhosis (n and %)	6	8
Chronic renal failure (n and %)	14	20
Valvular disease (n and %)	4	6
Ischemic heart disease (n and %)	16	23
Blood test data		
Hemoglobin level (g/dl) [mean, range]	7.5 +/- 2.25	
Prothrombin time (%) [mean, range]	82.9 +/- 22	
Platelets count (elts.10^3/mm^3) [mean, range]	227 +/- 88	
Drug use	**(n)**	**(%)**
Anticoagulant (n and %)	13	18
Antiplatelets (n and %)	16	23
Both (n and %)	3	4

Patients were referred for endoscopy to investigate either overt gastrointestinal bleeding (n=52) or anemia (n=17). Overt bleeding consisted of hematemesis in 3 cases, melena in 34 cases and hematochezia in 18 cases.

The sites involved in angiodysplastic lesions were: gastric in 18 cases (26%), small bowel 14 (20%), colon 53 (77%), including predominantly the right colon and cecum (47 cases or 68%). Lesions were localized to more than one site in 14 cases (20%). Lesions were single in 15 cases and multiple in 54 cases (78%). Sixteen patients had severe disease with a high number of angiodysplasias (>20). The mean size of the lesions was 5.7mm [range: 1–30mm]. Associated digestive lesions were found in 27 cases (39%) (table 2). However, the presence of active bleeding or stigmata of recent bleeding in angiodysplastic lesions led us to considere these lesions as the bleeding source.

The median number of treatment sessions was 1.49 [range: 1–5]. Forty six patients (66%) needed just one APC session.

The median number of lesions treated per session was 4.6 [range: 1–10] and argon plasma coagulation was performed within a mean of 1.6 months after bleeding.

Table 2 : Coexistent conditions contributing to anemia (n=27)

Disorder	**(n)**	**(%)**
Chronic renal failure	14	20
Drug use	26	37
Portal hypertension	6	8.6
Other gastrointestinal lesions susceptible to bleed	27	39

The characteristics of angiodysplasias are summarized in table 3.

Table 3: Characteristics of angiodysplastic lesions

Parameters of angiodysplastic lesions	**(n)**	**(%)**
Number		
- Single (n and %)	15	22
- Multiple (n and %)	54	78
Size (mm) [median +/- SD]	3 +/- 6.3	3 +/- 6.3
Location	**(n)**	**(%)**
- Caecum and right colon (n and %)	53	77
- Transverse colon (n and %)	4	5,7
- Left colon and rectum (n and %)	7	10
- Small bowel (n and %)	14	20
- Stomach (n and %)	18	26
Multiple locations	14	20
Number of APC sessions [median +/- SD]	1 +/- 0.8	
Number of lesions treated per APC session [mean - range]	4.6 [range: 1 – 10]	

In a total of 103 APC sessions, two complications occured: one submucosal hematoma which regressed spontaneously and one colonic perforation in a patient having ischemic and valvular disease. The outcome was the death of the patient despite emergency surgery (hemicolectomy). During endoscopy, two patients (who were taking antiplatelet agents) developed digestive hemorrage, but the outcome was good after endoscopic hemostasis (adrenalin injection). No colonic pneumatosis was observed.

2/ Efficacy of endoscopic treatment:

Forty-six patients required transfusion with median pretreatment hemoglobin level of 7.3 g/dL [range: 1.9–10] and mean corpuscular volume of 78.2 μ3 [range: 61.1–102]. The median pretreatment transfusion required (calculated as the average number of units used) was 2.5 [range: 0–14]. After APC treatment, the median hemoglobin level at follow-up was 9.3 g/dL [range: 5–13.5] (p value = 0.0001) and the median mean corpuscular volume was 82 μ3 [range: 61–99] (p value=0.001) on average. The median transfusion requirement after APC therapy was 0.1 packed red cells [range 0 – 4] (p value <0.0001). Thus, the transfusion requirement was effectively abolished for the majority of patients (43/46, 93%). Iron supplementation was given to respectively 25, 24 and 41 patients, before, between and after APC sessions (table 4).

Angiodysplasias were eradicated in 61 patients (88%) with an average follow-up time of 17.3 months [range: 2-72 months]. Based on univariate analysis, the predictive factors of recurrent bleeding after APC were the presenting bleeding symptom (melena) (p=0.032), ischemic heart disease (p=0.001), past medical history (p=0.007), lesions in the small bowel (p=0.035) or in the stomach (p=0.042) and

presence of associated gastrointestinal lesions (p=0.044). In addition, the use of antiplatelet therapy or anticoagulantion were also predictors of rebleeding with p values of 0.034 and 0.048 respectively (table 5). There were no differences between the two groups concerning age, sex ratio, alcohol or smoking habits, size and number of lesions. In multivariate analysis, none of these factors was significant.

Table 4: Variation of biological parameters and transfusion requirement

Parameter	Before APC	After APC	p value
Hemoglobin level (g/dL)	7.3 [range: 1.9 – 10]	9.3 [range: 5 – 13.5]	0.0001
Mean corpuscular volume (µ3)	78.2 [range: 61.1 – 102]	82 [range: 61 – 99]	0.001
Transfusion requirement (packed blood cells)	2.5 [range: 0 – 14]	0.1 [range: 0 – 4]	<0.0001
Iron supplementation (n=)	25	41	NS

Recurrence was observed in 23 patients (33%) after a mean time of 12.2 months [range: 1-30]. Therefore the efficiency of the APC in our study was 67%. Recurrence was revealed by overt bleeding in 14 cases (61%) and drop in hemoglobin level in 19 patients (83%). The mean hemoglobin level during the recurrence was 7.7 g / dl [range: 4-9.6]. Rebleeding was treated by repeated APC sessions in 21 cases (91.3%) and 8 patients relapsed after the second session, requiring respectively 3, 4 and five APC sessions in 4, 2 and one cases. A selective radiological embolization was performed in one case (4%) and surgical resection of the segment responsible for digestive bleeding was needed in 3 cases (13%). The outcome was favorable after surgical treatment in 3 cases. The summary trial of our cohort is represented in figure 2.

In the group of patients who had past medical history of cardiac ischemic or valvular disease or chronic renal failure (n=34), recurrence of bleeding was observed in 44 % of cases while such recurrence was only observed for 8 patients (22%) without medical history (p=0.007). Surgical treatment was required only for one patient after failure of radiological embolization. Thus, endoscopic treatment by APC has avoided surgery in 97% of patients with severe past medical history (n=33).

Figure 2 : Trial summary

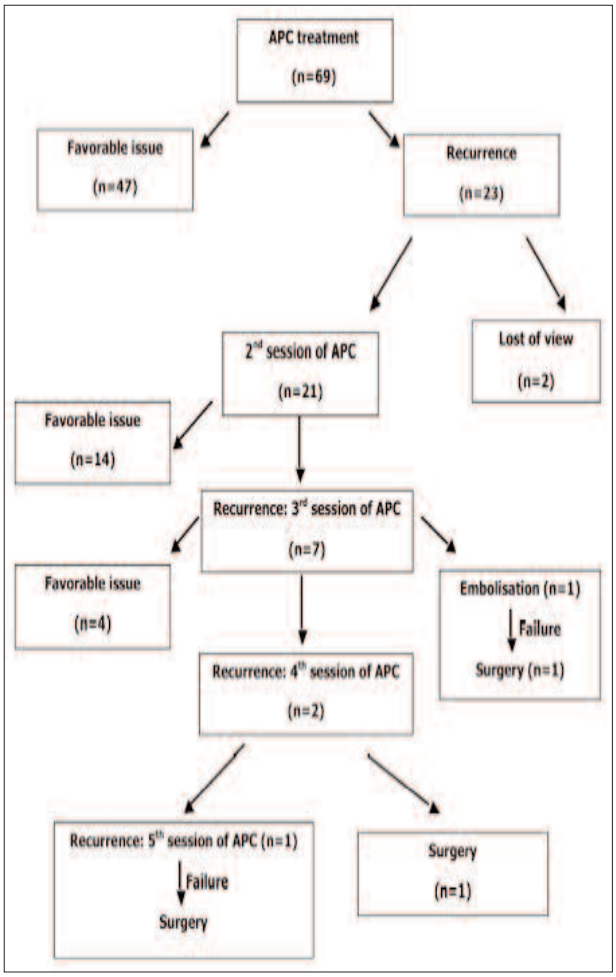
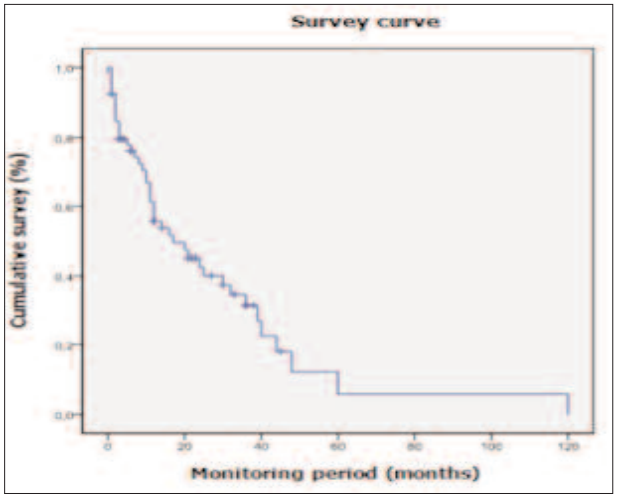


Table 5: Univariate analysis of the associations of individual parameters with recurrent bleeding in patients with bleeding angiodysplasia

Parameter		Eradication		p	Recurrence		p
		Yes (n=61)	No (n=8)	value	Yes(n=23)	No(n=46)	value
clinical							
	Melena	30	4	NS	16	19	0.03
Past medical history							
	Ischemic heart disease	13	3	NS	13	3	0.001
	Any past medical fact	30	5	NS	15	20	0.007
Drug consumption							
	Antiplatelet agents	14	2	NS	10	6	0.03
	Anticoagulant or antiplatelets or betablockers	29	6	NS	15	20	0.04
Characteristics of angiodysplasia							
Site:	Small bowel	3	21	NS	3	11	0.03
	Stomach or duodenum	0	2		0	10	0.04
	Associated lesions	25	2	NS	6	21	0.04

The mean follow-up time of the patients was 17.3 months [range: 0–190]. During follow-up, 7 patients died and 5 patients were lost to follow-up. No patients died from gastrointestinal bleeding. Causes of death were related to the underlying diseases. Two cirrhotic patients died, one of liver dysfunction and the other of hepatorenal syndrom. Three patients with renal or cardiac failure died from acute pulmonary edema. One patient died from small bowel ileus. Fifty four patients were included into the survey analysis. Survival without rebleeding was of 50% at 12 months and 42% at 24 months. The survival curve without rebleeding according to the Kaplan-Meier method is represented in fig 3.

Figure 3 : Survival curve without recurrence (Kaplan Meier method)



DISCUSSION

In our study, the efficacy of APC was evaluated based on hemoglobin level, reduction of transfusion requirements and recurrence rate after APC. APC treatment helped to avoid bleeding as evidenced by the significant rise in hemoglobin value from 7.3 to 9.3 g/dl (p=0.0001). It was also associated with a statistically significant reduction of transfusion requirements from 2.5 to 0.1 packed red cells (p<0.0001). Recurrence of bleeding was observed for 33.3% of patients (n=23) after a mean time of 12.3 months.

These data are comparable to results from previously published studies. Olmos and al. reported an increase of hemoglobin level from 8.6 g/dL to 12 g/dL with lower recurrence rate of 14% in the follow-up (2). Other working groups were able to present even higher success rates with lower recurrence rates in follow-up (3, 4).

APC is a relatively new technique that has many advantages (5). The cautery unit is compact, mobile and easy to maintain. The technique is simple to perform and easily learned. It is a non-contact thermal method of hemostasis that uses argon plasma to transfer electrical energy to the target tissue (6). It allows tangential application and thus treatment of the target site in a uniform manner to a depth of approximately 1 to 3 mm, which is sufficient to coagulate the superficial blood vessels (7). Successful APC therapy leads to whitish coagulation of the mucosa and the disappearance of the underlying vascular structures. The coagulation depth of APC depends on the power generator settings, the distance from the target tissue and the duration of the application (8). Variable power settings (30–100 W) and flow rates of argon gas (0.8–2 liter/min) have been reported to be safe and effective for hemostasis of bleeding vascular ectasia (9). To our knowledge, there are no publications comparing various power settings and flow rates, in terms of safety and efficacy of the application. An experienced gastroenterologist can adjust the distance between the APC probe and the target lesion and the duration of application to achieve a satisfactory effect at a variety of settings. Therefore, the operator's experience and technique are crucial to successful APC treatment. In our serie, there was only one main complication (colonic perforation) related to APC in the 103 treatment sessions, performed on the 69 patients. APC characteristics include rapid treatment of multiple or extensive lesions and decreased depth of penetration. However, all the complications that have been reported with other thermal hemostasis techniques, such as submucosal emphysema, superficial ulceration, fibrotic contracture, stricture and perforation, can still occur (10). The perforation rate has been reported to range from 0% to 8% and occurs most frequently when APC is used for ablation of Barrett's esophagus and palliative ablation of malignant stenosis (7, 11). In the Eickhoff serie (12), no major complication was noted while minor complications (fever, pain) were reported in 6 patients. In our case, the perforation was located in the right colon and occured in a patient with severe comorbidities. The use of a low energy output helps to minimize the risk of perforation in thin-walled areas, like the small intestine or the right colon, where angiodysplasias often occur. Other approaches to reduce the feared risk of perforation due to APC have been evaluated as well. The utility of obtaining a submucosal saline solution cushion before APC therapy to prevent deep tissue injury has been demonstrated in a porcine model and a clinical case series (13, 14). In our experience, in large angiodysplasia requiring a high amount of energy for complete ablation, or in those localized in thin-walled structures, submucosal injection before the APC procedure, with a saline solution with ou without adrenaline, in a proportion of 1:10000, can successfully be used to prevent complications such as perforation.

APC allowed to avoid surgery in 93.6% of patients with significant comorbidities (n = 47). Recurrence of bleeding was observed in 33.3% of the patients (n = 23) after a mean time follow-up time of 12.3 months. Based on evidence provided by Junquera et al (15), the follow-up period of the current study was adequate for assessment of the long-term efficacy of APC. Although the natural history of bleeding angiodysplasia remains to be fully established, it is generally accepted that bleeding is usually intermittent, with remissions and recurrences over time (16). In the study of Junquera et al (15), the placebo group had a 36% (95% CI [14%, 58%]) actuarial probability of remaining free of bleeding recurrence after 2 years. The variability in the natural history of bleeding GI angiodysplasias makes it difficult to evaluate the efficacy of any form of treatment, if the follow-up time is short (17). The present study also has some limitations, largely because of the absence of a control group. This could most likely lead to an overestimation of the efficacy of APC. This drawback is significantly reduced by a well-designed study. We feel that the result of our study is valid, because the design is based on current clinical practice.

CONCLUSION

APC is a highly effective and safe technique in the management of symptomatic bleeding from gastrointestinal vascular lesions. It assures a significant reduction of transfusion requirement and a significant increase in the hemoglobine level after treatment. This study is particularly interesting because it showed effective results in 97% of the patients with major comorbidities illnesses. The technique is safe and can be used without undue risk, even for patients with substantial comorbidities such as chronic renal failure or ischemic heart disease. APC should therefore be considered as the first-line endoscopic therapy in gastrointestinal angiodysplastic lesions.

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