Endoscopic resection is effective for the treatment of bleeding gastric hyperplastic polyps in patients with and without cirrhosis

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Background and study aims: Gastric hyperplastic polyps (GHP) have been identified as a cause of transfusion-dependent iron-deficiency anemia (tIDA) and transfusion-dependent gastrointestinal bleeding and are commonly identified in the setting of cirrhosis. The aim of this study was to assess the effectiveness of endoscopic resection (ER) for the treatment of tIDA or gastrointestinal bleeding due to GHP in patients with and without liver disease.

Patients and methods: This was a single-center retrospective review. The primary outcome was clinical success of ER (no transfusion or repeat ER in the following 6 months after first ER). Secondary outcomes included technical success, recurrence of GHP with tIDA or gastrointestinal bleeding, and adverse events (AEs).

Results: Sixty-three patients with GHP were included of whom 20 (31%) had cirrhosis. The majority with cirrhosis presented with gastrointestinal bleeding (n=13, 65%, P=0.52), whereas the majority of non-cirrhotics presented with tIDA (n=30, 70%, P=0.01). Technical success was 100% with no AEs. The clinical success rate was 94% (95% in cirrhotics, 93% in non-cirrhotics, P=0.46). The recurrence rate was 32% (40% in cirrhotics and 28% in non-cirrhotics, P=0.35) with mean time to recurrence of 17.3±13.9 months (P=0.22). Of those with recurrence, 75% had no further tIDA or gastrointestinal bleeding after repeat ER (mean follow-up 20 ±11 months).

Conclusions: ER is an effective treatment for GHP that causes tIDA or gastrointestinal bleeding. Patients with GHP and cirrhosis tend to present with bleeding rather than anemia and have more frequent recurrence. Symptomatic recurrence of GHP is common and should be recognized early as repeat ER appears to be effective.

Introduction

Gastric polyps are detected in 6% to 8% of all upper endoscopic exams with the majority of polyps being classified as fundic gland polyps (77–80%) and hyperplastic polyps (17–19%) [1,2]. As recently as 10 to 15 years ago, hyperplastic polyps were recognized as the most common type of gastric polyp; however, the distribution has been influenced by use of proton-pump inhibitors (PPI) [1,3]. Gastric hyperplastic polyps (GHP) have been identified as a cause of transfusion-dependent iron-deficiency anemia (tIDA) or obscure gastrointestinal bleeding and are more commonly seen in patients with chronic gastritis (e.g. Helicobacter associated) [3–5]. While GHP have been identified as a cause of tIDA and gastrointestinal bleeding due to ulceration, overt gastrointestinal bleeding is rare [2,5,6]. Although endoscopic resection (ER) has been described for resection of large GHP, there are no data regarding its clinical impact on gastrointestinal blood loss.

The prevalence of GHP in patients undergoing esophagogastroduodenoscopy (EGD) is estimated to be about 1% in patients with cirrhosis (**Fig. 1**) [7]. Due to this infrequent occurrence there have been few studies describing GHP in portal hypertension. However, when combined with increased vascular pressures and coagulopathy associated with liver disease, the incidence of bleeding or symptomatic anemia appears to increase [6,8]. GHP arising in the setting of liver disease may have differing pathophysiology and phenotypes than that in otherwise healthy patients, notably increased vascularity [8]. Thus, a disproportionate number cirrhotic patients may experience clinically significant blood loss associated with GHP.

Current management of GHP incudes endoscopic removal of polyps that are large, symptomatic (evidence of blood loss or outlet obstruction), or dysplastic [9,10]. We hypothesized that ER of GHP is a safe and effective treatment for tIDA or gastrointestinal bleeding in patients with and

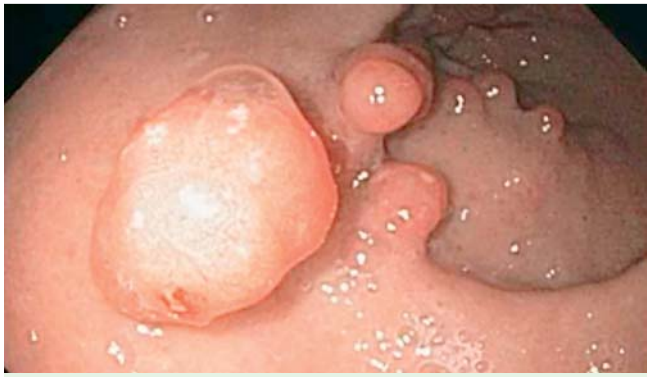

Fig. 1 Endoscopic appearance of gastric hyperplastic polyps.

without liver disease. The primary aim of this study was to assess the clinical success of ER for GHP in patients with cirrhosis compared to a control population without liver disease. Secondarily, we assessed technical success, rates of recurrence, and adverse events of ER for GHP.

Patients and methods

Study design

We performed a retrospective cohort study of all patients undergoing ER for GHP between 2008 through 2014 at a single academic medical center. Patients were identified via review of a prospectively maintained endoscopy database. This study was approved by the institutional review board at Northwestern University.

Study population

All patients referred for ER of gastric polyps with concurrent tIDA or overt or obscure gastrointestinal bleeding over the study period were identified. Transfusion dependence was defined as requiring at least 2 units of packed red blood cells on a monthly basis. Cirrhosis was confirmed either by abdominal imaging or liver biopsy. Only patients with signs of portal hypertension (e.g., esophageal varices, gastric varies, splenomegaly, ascites, or portal hypertensive gastropathy) were included in the "cirrhosis" cohort.

Endoscopic resection

ER of GHP was performed using a standard submucosal injection and resection technique. Polyps that were a potential source of bleeding were resected at the discretion of the endoscopist, regardless of size. Each polyp was injected with indigo carmine or methylene blue with or without dilute epinephrine and saline. The polyps were resected using standard hexagonal or oval snares en bloc. All defects were closed with hemostatic clips to prevent delayed bleeding (**Fig. 2**).

Clinical data

A review of the patient's electronic health record was performed to abstract relevant demographic and clinical characteristics. Patient demographics were recorded including age and gender. The presence of liver disease was recorded in addition to other comorbid conditions including portal hypertensive gastropathy, gastric antral vascular ectasia (GAVE), familial polyposis syndromes, and *Helicobacter pylori* infection (determined by surgical pathology). Use of PPIs, beta blockers, alcohol, tobacco, and anticoagulation in addition to international normalized ratio (INR) were also recorded. Endoscopy data collected included location, gross size, number of polyps resected, and adverse events (AEs). Histology was reviewed for dysplasia or malignancy. A single hemoglobin value was recorded immediately prior to the procedure and repeat levels were obtained periodically after ER. We included data for the earliest hemoglobin levels collected at least 6 months post-ER unless a repeat procedure was required at which time we included data for hemoglobin levels obtained just prior to that ER.

Primary outcome measures

The primary outcome was clinical success as defined by no further blood transfusions or need for repeat ER in the following 6 months after ER. Secondary outcomes included technical success of ER (complete resection of target GHP without any peri-procedural complications), recurrence (need for transfusion or repeat ER at any time after initial ER) and AEs associated with ER of GHP.

Statistical analysis

Appropriate descriptive statistics were performed. Univariate analyses between groups were performed using the student's t-test for continuous variables and Fisher's exact test and chi-squared analysis for dichotomous variables. A P value <0.05 was considered statistically significant. Data analysis was performed using SPSS 22.0 (IBM Corp. Armonk, NY).

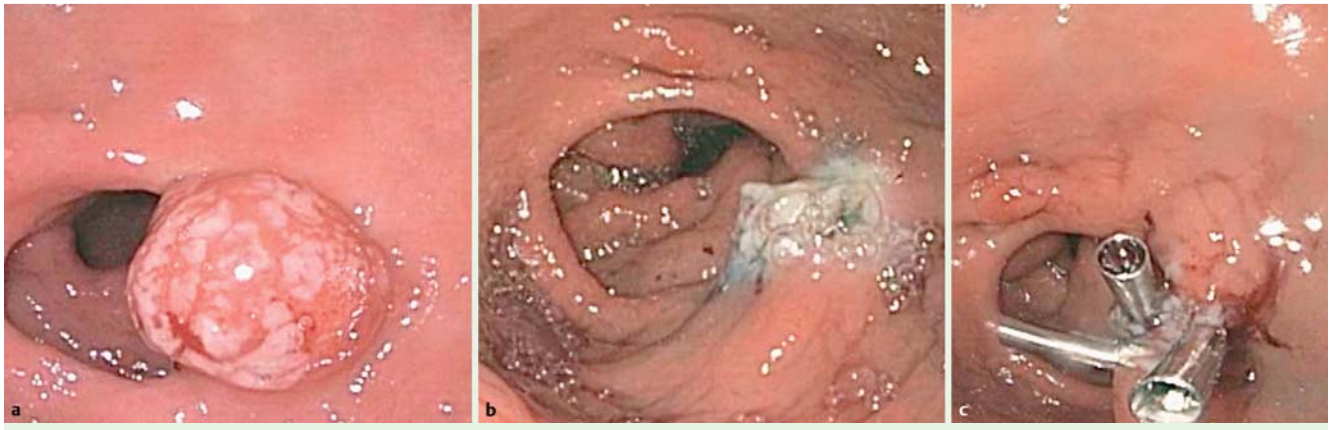

Fig. 2 Endoscopic mucosal resection of gastric hyperplastic polyps. **a** Pre-resection. **b** Post-resection. **c** Hemostatic clip closure.

Characteristic	Non-cirrhotic	Cirrhotic	Overall	*P* value
Age at time of ER (SD)	65.3 (13.4)	63.4 (10.1)	64.7 (12.4)	0.41
Male gender	22 (51)	11 (55)	33 (54)	0.16
Smoking (n, %)	4 (9)	0 (0)	4 (6)	0.46
Significant Alcohol (n, %)[1]	5 (12)	1 (5)	6 (10)	0.24
MELD (SD)	n/a	12 (3.8)	n/a	n/a
Beta-Blocker (n, %)	n/a	20 (100)	n/a	n/a
PPI Use (n, %)	28 (65)	16 (80)	44 (70)	0.31
Anticoagulation (n, %)	22 (51)	8 (40)	30 (48)	0.33
Aspirin only (n, %)	11 (26)	4 (20)	15 (24)	0.18
Plavix (n, %)	3 (7)	0 (0)	3 (5)	0.13
Therapeutic (n, %)[2]	8 (19)	4 (20)	12 (19)	0.22
Mean INR (SD)	1.2 (0.5)	1.3 (0.2)	1.2 (0.4)	0.82
H. Pylori (n, %)	9 (21)	3 (15)	12 (19)	0.28
Portal Hypertensive Gastropathy (n, %)	0 (0)	1 (5)	1 (2)	n/a
GAVE (n, %)	1 (2)	1 (5)	2 (3)	n/a
Gastric Varices (n, %)	0 (0)	2 (10)	2 (3)	n/a

Table 1 Demographics and clinical characteristics.

[1] Significant alcohol use was defined as greater than one drink per day for females and greater than two drinks per day for males.
[2] Therapeutic anticoagulation included warfarin, enoxaparin, and novel oral anticoagulants.

Characteristic	Non-cirrhotic	Cirrhotic	Overall	*P* value
Mean number of polyps resected (SD)	2.7 (2.2)	3.2 (2.0)	2.8 (2.1)	0.36
Mean polyp size mm (SD)	18.3 (10.4)	17.4 (9.7)	18.0 (10.2)	0.11
Location by percentage				
Cardia	15	14	14	0.87
Fundus	6	5	6	0.52
Body	28	32	29	0.21
Antrum	40	41	41	0.93
Pylorus	11	9	10	0.45
Dysplasia on histology (%)	3 (7)	0 (0)	3 (5)	n/a

Table 2 Polyp characteristics.

Results

Patient characteristics

Sixty-three patients were identified who underwent ER of GHP over the 7-year period, 31% (n=20) with cirrhosis. There were no significant differences amongst baseline characteristics and comorbidities between the 2 groups (**Table 1**). A majority of patients (n=13, 65%) with cirrhosis presented with gastrointestinal bleeding (*P*=0.52), whereas the majority of non-cirrhotics (n=30, 70%) presented with tIDA (*P*=0.01). The mean hemoglobin prior to ER was similar in cirrhotics (10.6±2.5) and non-cirrhotics (11.2±1.8, *P*=0.45). All patients with cirrhosis had clinical evidence of portal hypertension and were on a non-selective beta blocker; 4 (20%) had other potential sources of gastrointestinal blood loss. The average Model for End Stage Liver Disease (MELD) score of patients with cirrhosis was 12±3.8. The majority of patients with cirrhosis were Child-Pugh Class B (Class A n=1; Class B n=14, Class C n=3, Inadequate data n=2).

Polyp distribution and histology

The mean number of polyps resected was 2.8 (SD 2.1) and the mean polyp size was 18.0 mm (SD 10.2) without significant difference between groups. The polyps were predominantly located in the antrum (41%). There were 3 cases of dysplasia or malignancy and all were in patients without cirrhosis (**Table 2**).

Technical and clinical success of endoscopic resection

The technical success rate for ER was 100%. The clinical success rate for ER (defined as no requirement for transfusion or repeat ER for 6 months) was 94%. This did not differ significantly between cirrhotics (95%) and patients without cirrhosis (93%, *P*=0.46). Clinical success was not associated with number of polyps, size of polyps, or coagulopathy. The overall rate of recurrence of gastrointestinal blood loss (need for transfusion or repeat ER) was 32% and did not differ between cirrhotics and non-cirrhotics (n=8, 40% vs. n=12, 28%, *P*=0.35). The mean time to recurrence was 17.3±13.9 months and did not differ between groups (*P*=0.22). Of the 20 patients who had recurrent gastrointestinal blood loss attributed to GHP, all underwent repeat endoscopy and 75% had no further evidence of tIDA or gastrointestinal bleeding (mean follow-up 20±11 months, median follow-up 22 months with interquartile range 12.5) after repeat ER (**Table 3**). There were no AEs on initial or subsequent ER.

Discussion

In the current study we report that ER is effective for the removal of GHP causing tIDA or overt gastrointestinal bleeding. Furthermore, the outcome did not differ between patients with and without cirrhosis.

It has been reported that 15% to 17% of patients with GHP have concurrent anemia and that removal of GHP can improve hemoglobin levels [1,2,6]. In this investigation of patients with GHP, 94% had resolution of tIDA or gastrointestinal bleeding in the following 6 months after ER. Furthermore, the initial effect of ER appears durable as demonstrated by a mean time to symptomatic recurrence at 17.3 months. This effect was consistent in patients with and without cirrhosis, despite cirrhotic patients presenting with lower hemoglobin levels. Symptomatic recur-

Characteristic	Non-cirrhotic	Cirrhotic	Overall	*P* value
Presenting with gastrointestinal bleeding (n, %)	13 (30)	13 (65)	26 (41)	0.52
Presenting with tIDA (n, %)	30 (70)	7 (35)	37 (59)	0.01
Mean hemoglobin prior to first ER g/dL (SD)	11.2 (1.8)	10.6 (2.5)	11.0 (2.1)	0.45
Mean hemoglobin after first ER g/dL (SD)	12.1 (1.8)	11.7 (2.3)	12.0 (2.0)	0.31
Mean change in hemoglobin g/dL (SD)	0.9 (1.7)	1.1 (2.6)	1.0 (2.0)	0.14
Mean months until repeat hemoglobin (SD)	15.2 (19.2)	12.5 (6.9)	14.3 (16.2)	0.136
Recurrence (n, %)	12 (28)	8 (40)	20 (32)	0.35
Clinical success (n, %)	40 (93)	19 (95)	59 (94)	0.46
Adverse events (n, %)	0 (0)	0 (0)	0 (0)	n/a
Mean time to recurrence months (SD)	17.8 (17.2)	16.4 (6.4)	17.3 (13.9)	0.22

Table 3 Clinical presentation and outcomes of endoscopic resection.

rence was common as a considerable number of patients (32%) ultimately had return of tIDA or gastrointestinal bleeding requiring transfusion and repeat ER with a trend towards more frequent recurrence in the presence of cirrhosis. Of the 20 patients who had recurrence, only 5 had persistent bleeding after the second treatment, suggesting that repeat endoscopic therapy is effective for treatment of GHP.

Nearly one-third of patients in this study had cirrhosis, which is similar to the rate reported by Al-Haddad et al. in his series of bleeding GHP (29%) [6]. It remains unclear if this is indicative of an increased incidence of GHP in cirrhotics or simply due to an increased propensity for bleeding. In a series of 611 patients with cirrhosis undergoing EGD for screening or surveillance of varices, De Lisi et al. found gastric polyps in 20 patients (3.3%) of whom 7 (35%) were hyperplastic [7]. This is similar to results from a study in India of patients with portal hypertension in which polyps were present in 2.53% of patients of whom 29% were hyperplastic [11]. These studies represent a lower prevalence of gastric polyps than in the general population, but a similar overall rate of GHP in cirrhotics and non-cirrhotics.

The precise pathophysiologic mechanism as to why GHP occur in liver disease is unclear. Lam et al investigated a series of 12 patients with GHP in the setting of portal hypertension and found similar histology as control patients except for distinctly more vascular and less foveolar proliferation [8]. They proposed that portal hypertension induces vascular alterations with foveolar growth as a secondary change. Others have hypothesized that they are simply GHP arising on a background of vascular changes associated with portal hypertension, although the majority of patients in the current study did not have PHG or GAVE [12]. However, increased vascularity could contribute to a higher potential for bleeding. In the current study, patients with cirrhosis were more likely to present with gastrointestinal bleeding as opposed to tIDA and with lower hemoglobin levels, although the latter may be accounted for by other sequelae of liver disease. Given similar rates of clinical success, recurrence, and change in hemoglobin between groups, it is unclear if the differences in presentation are due to higher bleeding risk within the polyp or attributable to other reasons for gastrointestinal blood loss or anemia in cirrhosis.

There are a few limitations of this study including a retrospective design. Data on the exact magnitude of red blood cell transfusions beyond a monthly requirement were not available. Follow up was assessed as return appointments within the institution and some patient data were not available due to follow up in other health systems. Finally, there may be a selection bias in that patients more likely to benefit from ER were referred for treatment.

In summary, ER is an effective treatment for GHP that causes tIDA or gastrointestinal bleeding. Patients with GHP and concurrent cirrhosis tend to present with bleeding rather than anemia and have more frequent recurrence than do their non-cirrhotic counterparts. Symptomatic recurrence of GHP is common and should be recognized early as repeat ER appears to be effective.

Competing interests: None

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