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Endoscopic Eradication of Esophageal Varices Transiently Affects the Development and Severity of Portal Hypertensive Gastropathy

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1. Abstract

The impact of esophageal varices treatment on portal hypertensive gastropathy and its subsequent clinical course must be investigated. We evaluated whether esophageal varices eradication affects the onset and severity of portal hypertensive gastropathy. Twenty-one patients (seven women; average age, 65.2 ± 11.3 years) who underwent endoscopy >1 month before esophageal varices endoscopy and another endoscopy within 14 days after esophageal varices treatment were included. Follow-up endoscopy evaluated findings at least 3 months after treatment. For cases treated multiple times, endoscopic findings after the last treatment were evaluated. Treatment comprised endoscopic varicose vein ligation for 21 patients. The grade of portal hypertensive gastropathy was grade 0 in 10 cases, grade 1 in 5 cases, and grade 2 in 6 cases, 3 months before follow-up. There were five newly developed (23.8%), five exacerbated portal hypertensive gastropathy cases (23.8%), and 12 cases with no changes (52.4%). Of the nine patients with newly developed or exacerbated portal hypertensive gastropathy, five patients showed improvements of portal hypertensive gastropathy after 3 months of follow-up. Of the five patients, two showed total disappearance of portal hypertensive gastropathy. Finally, of the 19 patients followed up during this study, 11 patients had no improvements in portal hypertensive gastropathy grade; the condition worsened in five and improved in three. Esophageal varices eradication may affect the onset and progression of portal hypertensive gastropathy immediately after treatment. No cases with severe bleeding from portal hypertensive gastropathy lesions have been identified.

2. Introduction

Portal Hypertensive Gastropathy (PHG) and Gastric Antral Vascular Ectasia (GAVE) are common and characteristic findings in Liver Cirrhosis (LC) patients [1−6]. Both PHG and GAVE cause anemia, acute or insidious gastrointestinal bleeding, and Esophageal Varices (EV) [7-11]. Therefore, the management of PHG and GAVE is an important issue for LC patients.

The natural history of PHG is unclear. Some studies have found that PHG is a progressive disease [7, 12]. However, other studies have found that PHG may regress in a moderate proportion of patients [13-15]. Many previous studies have evaluated the severity of liver disease [16-19], etiology of liver disease [20, 21], duration of liver disease [9, 17], presence of EV [8, 22-27], and the procedures that lead to the eradication of EV. Furthermore, numerous studies have demonstrated that the incidence and/or severity of PHG can increase after EV eradication [14, 24-27]. Recently, decreases in the prevalence of EV and PHG have been reported, which may be related to improved treatments for LC and viral hepatitis as well as the decreased prevalence of viral hepatitis; however, the EV prevalence caused by alcoholic LC or Non-Alcoholic

Steatohepatitis (NASH) might have increased [28-30]. Therefore, it is important to investigate the effects of EV treatment on PHG and its subsequent clinical course. This study evaluated whether EV eradication influenced the development and severity of PHG at our institution.

3. Materials and Methods

This single-center retrospective study evaluated 21 Japanese patients (7 women and 14 men; mean age: 65.2 ± 11.3 years) who had undergone endoscopy more than 1 month before endoscopic treatment of EV and subsequently underwent endoscopy less than 14 days after EV treatment. All patients had been treated between April 2011 and Jun 2019. The retrospective protocol of this study was approved by our institutional review board, and all patients provided written informed consent for the publication of this report. Follow-up endoscopy findings were evaluated ≥3 months after treatment. If the patient received more than one treatment, then endoscopic findings of the last treatment were evaluated. PHG severity based on endoscopic findings was classified as grade 0 (no related findings), grade 1＝mild (fine pink speckling [scarlatina-type rash] and mosaic pattern [snakeskin appearance]), grade 2=severe (discrete-red spot, diffuse hemorrhagic lesion) according to the classification described by McCormack et al. [31]. All endoscopic findings regarding PHG were retrospectively evaluated by three expert endoscopists (K.H., K.N., and N.Y.). In addition, we investigated the relationship between changes in PHG after EV treatment and age, sex, background liver, child hue classification, EV and RC status, presence or absence of gastric varix, splenomegaly and collateral hemodynamics.

3.1. Assessment of Splenomegaly and Collateral Circulation

Splenomegaly was assessed by ultrasound imaging. Splenomegaly is defined as the product of the diameter from the hilum to the anterior margin of the spleen and the perpendicular diameter of >20 cm^2. The collateral circulation was evaluated by abdominal CT, and the diagnosis of Left Gastric vein Shunt (LGS) was defined as ≥5 mm, and the diagnosis of Spleno-Renal Shunt (SRS) was defined as ≥8 mm.

3.2. Statistical Analysis

For statistical analysis, a χ-square test was performed on categorical variables and a Shapiro-Wilk test was performed on continuous variables for comparison between the two groups. A P-value < 0.05 was considered significant. All statistical analyses were performed using JMP Statistical Software (version 14.2, SAS system, USA).

This study was approved by the Kawasaki Medical School Ethics Committee (approval number 5105). This study was conducted in accordance with the principles laid out in the Declaration of Helsinki (1964).

4. Results

Treatments comprised endoscopic variceal ligation for 21 patients. The average grade of portal hypertensive gastropathy was grade 0 in 10 cases, grade 1 in 5 cases, and grade 2 in 6 cases 3 months before follow-up. The Child-Pugh scores were 5-6 points, 7-9 points, and 10-15 points in 12 cases, 7 cases, and 2 cases, respectively. All pre-treatment EVs were F2 or F3, and 17 patients had RC signs. Gastric varices were also found in 11 cases. In addition, LGS was found in three cases, SRS was found in one case, and splenomegaly was found in all cases (Table 1). Follow-up endoscopy was performed in 21 patients 2 weeks after treatment and 19 patients 3 months or more (Table 2). Two weeks after treatment, there were five newly developed (23.8%), four exacerbated portal hypertensive gastropathy cases (19%), and 12 cases with no changes (57.2%). In other words, there were nine cases in which PHG worsened and 12 cases in which PHG remained unchanged.

Table 1: Trends in portal hypertension gastropathy grades before and after endoscopic treatment of esophageal varices

Case	Sex	Age, (years)	Cause of LC	Child-Pugh score	Esophageal Varix		Gastric Varix				
					Form	RC	Form	RC	LGS	SRS	SI
1	F	72	NBNC	9	2	3	1	0			23
2	F	71	NASH	8	3	3	1	0	+		28
3	F	59	NASH	6	2	0	2	0	+		47
4	M	64	AL	6	2	0	1	0			27
5	M	69	AL	6	3	3	2	0			25
6	F	76	NASH	6	3	3	1	0			26
7	F	64	C	5	2	2	1	0			41
8	M	80	AL	8	2	0	-	-			40
9	M	70	AL	6	2	0	2	1			27
10	M	48	PBC	8	2	2	-	-			48
11	F	84	AIH	9	2	1	-	-			40
12	M	58	B	7	2	1	-	-			23
13	M	71	AL	5	2	3	-	-			33
14	M	64	C	10	2	3	-	-			88
15	M	55	B	10	2	3	1	0		+	28
16	M	70	AIH	6	2	2	-	-	+		39
17	M	44	C	5	2	3	-	-			40
18	F	77	C	6	3	3	-	-			20
19	M	40	AL	8	3	1	1	0			25
20	M	66	NASH	5	3	3	0	0-			28
21	M	67	AL	5	3	2	-				25

F: Female; M: Male; NBNC: nonB, nonC; NASH: Non-alcoholic steatohepatitis; AL: Alcoholism; C: Hepatitis C; PBC: Primary biliary cholangitis; B: Hepatitis B; AIH: Autoimmune hepatitis; LC: liver cirrhosis; PHG: portal hypertension gastropathy; LGS: Left gastric vein shunt; SRS: Spleno-Renal shunt; SI: Spleen Index; RC: red color sign.

Table 2: Trends in portal hypertension gastropathy grades before and after endoscopic treatment of esophageal varices

Case	Endoscopic grade			
	Before treatment	After treatment (after 2 weeks)	Follow-up (>3 months)	Endoscopy procedure, n
1	0	2	-	2
2	0	2	0	2
3	0	2	1	2
4	0	2	2	1
5	0	0	2	1
6	0	0	0	1
7	0	0	0	1
8	0	0	0	1
9	0	1	1	1
10	0	0	1	2
11	1	2	-	1
12	1	2	0	2
13	1	1	1	1
14	1	1	1	1
15	1	2	0	1
16	2	3	2	3
17	2	2	0	3
18	2	2	2	2
19	2	2	2	1
20	2	2	2	1
21	2	2	2	2

Among the nine patients with newly developed or worsened PHG, follow-up evaluations performed more than 3 months after treatment revealed PHG disappearance in two patients and PHG improvement in five patients. Among the five patients with no evidence of PHG immediately after treatment, two patients exhibited new PHG during the follow-up evaluation performed more than 3 months after treatment. Of the 19 patients followed up for more than 3 months, five patients had newly developed or worsened PHG compared to pretreatment findings. Eleven patients had no PHG grade changes, and three patients had improved PHG grades.

There was no relationship between changes in PHG after EV treatment and age, sex, background liver, hue classification of children, EV and RC status, presence or absence of gastric varices, splenomegaly, and collateral hemodynamics (Table 3a, b).

Table 3a: Changes and background of portal hypertension gastric disease grade before and after endoscopic treatment of esophageal varices (before treatment-2 weeks after treatment)

	PHG worse (n=9)	PHG no change (n=12)	P-Value
M/F	5/4	9/3	N.S
Age (years)	67±8	63±13	N.S
Child-Pugh score	7.4±1.5	6.4±1.6	N.S
EV form	2.1±0.3	2.5±0.5	N.S
EV RC (+/-)	6/3	11/1	N.S
GV (+/-)	6/3	5/7	N.S
LGS	0/9	1/11	N.S
SRS	2/7	1/11	N.S
Splenomegaly (+/-)	9/0	12/0	N.S

Table 3b: Changes portal hypertension gastric disease grade before and after endoscopic treatment of esophageal varices (before treatment-3 months after treatment)

	PHG worse (n=5)	PHG no change and decrease (n=14)	P-Value
M/F	4/1	10/4	N.S
Age(years)	62±8.7	64±11.7	N.S
Child-Pugh score	6.4±0.8	6.7±1.8	N.S
EV form	2.2±0.4	2.4±0.5	N.S
EV RC （+/-）	2/3	13/1	N.S
GV (+/-)	4/1	6/8	N.S
LGS	0/5	1/13	N.S
SRS	¼	2/12	N.S
Splenomegaly (+/-)	5/0	14/0	N.S

F: Female; M: Male; EV: esophageal varix; RD: red color; GV: gastric varix; LGS: Left gastric vein shunt; SRS: Spleno-Renal shunt; SI: Spleen Index; PHG: Portal hypertensive gastropathy; RC: red color sign.

Three experts performed endoscopic diagnosis, and the concordance rate was about 80%. Three experts have considered and decided on cases of inconsistency. For hepatitis C and B, there was no relationship between treatment time and PHG treatment time.

5. Cases

(Figure 1) shows a case in which PHG was exacerbated from mild to moderate immediately two weeks after treatment. Pretreatment endoscopic images revealed a snakeskin appearance; however, post-treatment images revealed a distinct cherry-red spot. (Figure 2) shows a case in which there was no PHG before and two week after treatment based on the endoscopic images. (Figure 3) shows a case of resolved PHG that involved typical moderate findings before treatment, a cherry-red spot both before and after two-week treatment, and no findings of PHG during follow-up endoscopy performed at 1 year and at 6 years and 3 months.

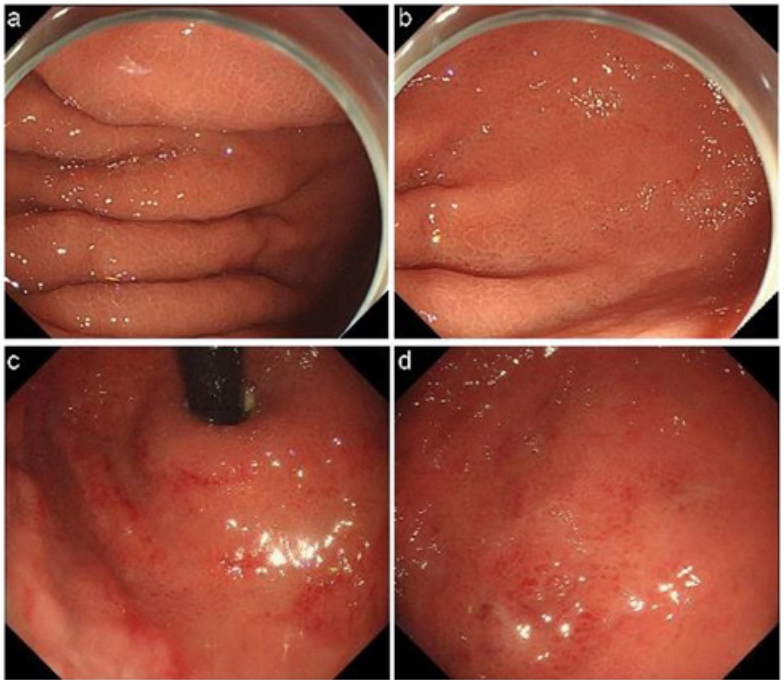

Figure 1: A case of portal hypertension gastropathy that exacerbated from mild to moderate immediately after treatment. The pretreatment endoscopic images (a, b) show a snakeskin appearance. The post-treatment images (c, d) show a distinct cherry-red spot.

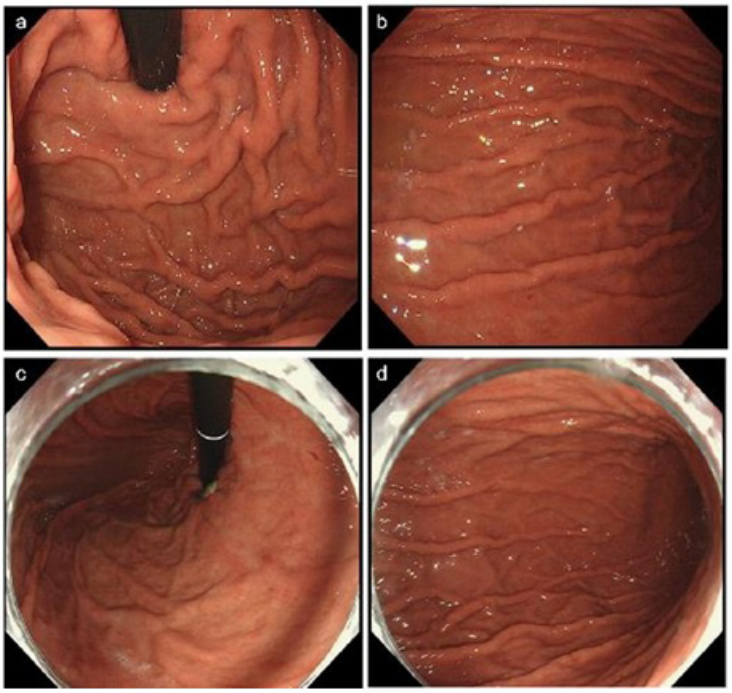

Figure 2: A case that did not involve portal hypertension gastropathy before or after treatment. There were no signs of portal hypertension gastropathy according to the pretreatment endoscopic images (a, b) and post-treatment images (c, d).

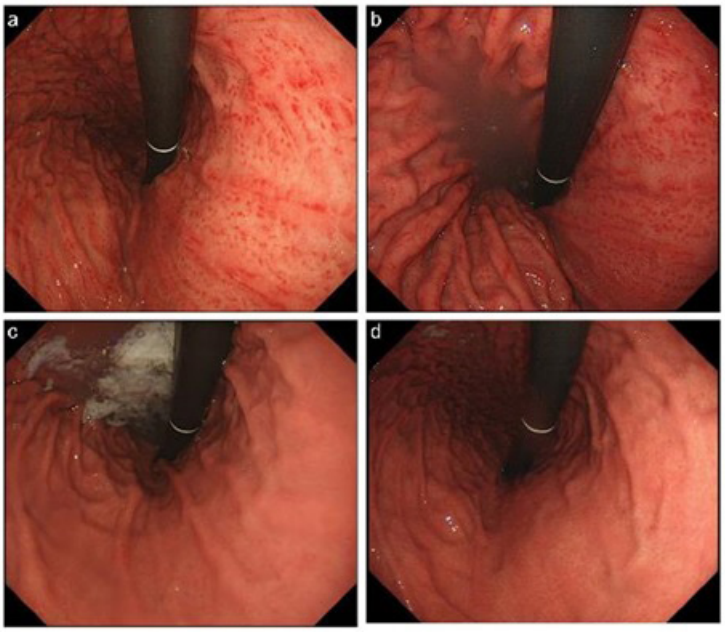

Figure 3: A case with portal hypertension gastropathy resolution. Pretreatment image (a) shows typical moderate findings. Immediate post-treatment image (b) reveals the typical presence of a cherry-red spot. No signs of portal hypertension gastropathy were observed after 1 year (c) or after 6 years and 3 months (d).

6. Discussion

Among 21 patients, 9 patients experienced new or worsened PHG immediately after EV eradication. Among 19 patients who were followed up for more than 3 months, five patients had new or worsened PHG relative to the pretreatment findings. Therefore, EV eradication might influence the development and progression of PHG immediately after treatment. Severe PHG disappeared in three patients. Furthermore, the average PHG score improved during the follow-up period. Therefore, it appears that PHG develops transiently after EV eradication. It is important to note that we did not identify any cases with serious bleeding from PHG lesions.

Many previous studies have indicated that EV eradication is a risk factor for the development and progression of PHG [14, 24-27]. Furthermore, a systematic review by Gjeorgjievski and Cappell revealed that that the incidence and severity of PHG increased after EV eradication [6]; this was likely related to an acute blockage of gastric mucosal blood flow. Nevertheless, Sarin et al. prospectively evaluated 967 patients with variceal bleeding who underwent successful eradication; they reported that PHG is often transitory and less severe after EV eradication [16. Perez et al. also reported that the endoscopic findings of severe PHG improved in 8 of 28 patients (30.8%) who received propranolol and in 5 of 28 patients (17.9%) who received placebo [32]. According to endoscopic findings, one of our patients also experienced PHG disappearance (from grade 2 to grade 0). Watanabe et al. reported that the portal blood pressure was lower in patients with fundal varices than in patients with isolated EV [14]. Iwao et al. reported that spontaneous and obliteration-induced PHG lesions developed less frequently in patients with cirrhosis and fundal varices [15]. However, our patient who experienced PHG disappearance did not develop fundal varices during the study period.

To the best of our knowledge, four Japanese studies have evaluated whether EV eradication influences the severity of PHG based on the classification system proposed by McCormack et al. [31] (Table 4). Iwao et al. evaluated 62 patients who underwent EV eradication and reported that the PHG scores of patients with poorly developed fundal varices increased at 3 months ($p<0.01$), 6 months ($p<0.01$), and 9 months ($p<0.05$) [16]; however, no significant changes in PHG were observed in patients with well-developed fundal varices [16]. We did not identify any patients with newly developed fundal varices. Tanoue et al. evaluated 137 patients with LC; they observed that PHG scores were significantly higher after endoscopic injection sclerotherapy and that PHG worsened at 6 to 9 months after EV eradication, followed by gradual improvement [33]. Yoshikawa et al. evaluated 35 patients with LC and reported that only two patients (5.7%) developed severe PHG, six patients (17.1%) developed mild PHG, and 27 patients (77.1%) exhibited no changes in the endoscopic appearance of PHG [34]. Hamada et al. performed a detailed follow-up of 56 patients with LC and reported that PHG had worsened in 34 patients (60.7%) at 1 month after treatment, improved slightly at 6 months and 12 months after treatment, and then worsened beyond its status before treatment [35].

Table 4: Japanese reports of endoscopic treatment of esophageal varices in the acute or chronic phase using McCormack's endoscopic classification

Author	Year	Patients (n)	Treatment method	Immediately after treatment	Follow-up
Tanoue *et al*.[33]	1992	137	EIS	NE‡	Worsened (6–9 months)
Iwao *et al.*[32]	1997	62	EVL§	NE	Worsened
Yoshikawa *et al.* [34]	1998	35	-	Newly developed (22.8%)	NE
Hamada *et al.* [35]	1999	56	EIS	NE	Worsened (60.7%)
Our study	2020	22	EVL, EIS	Newly developed (50%) and worsened (33.3%)	Newly developed (2), no change (12), and improved (4)

EIS: Endoscopic injection sclerotherapy; EVL: Endoscopic variceal ligation; NE: not examined; PHG: portal hypertension gastropathy; EV: esophageal varix

In this study, we examined various background factors, such as new appearance or worsening of PHG after EV treatment, improvement, disappearance, and unchanged cases, but there was no clear factor, probably because of the small number of cases. It is necessary to increase the number of cases and conduct further studies in the future. Interestingly, this study did not identify any cases of bleeding from PHG lesions immediately after EV eradication or during the follow-up period. This would imply that endoscopic treatment of EV exacerbates the findings of PHG but does not cause gastrointestinal bleeding. The difference between this finding and the findings of our previous studies of serious bleeding from PHG after EV eradication may be related to the preventative effects of proton pump inhibitors. The incidence of LC related to viral infection, which causes PHG, has been declining in Japan [29]; however, its incidence related to non-alcoholic steatohepatitis is increasing. Therefore, based on the findings of this study and previous studies, it is important to further investigate the natural history of PHG after EV treatment.

This study had several limitations. It was a retrospective analysis of a small sample of patients from a single-center, making it prone to bias.

7. Conclusions

In conclusion, EV treatment may affect the onset and progression of PHG. This study did not identify cases with severe bleeding from PHG lesions. However, after the EV treatment, a follow-up of EV and PHG lesions is highly recommended.

8. Data Availability

The data used to support the findings of this study are restricted by the Kawasaki Medical School Ethics Committee in order to protect patient privacy. Data are available from the corresponding author (Miwa Kawanaka; m.kawanaka@med.kawasaki-m.ac.jp) for researchers who meet the criteria for access to confidential data.

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