USEFULNESS OF ENDOSCOPIC ULTRASONOGRAPHIC ANALYSIS OF VARICEAL HEMODYNAMICS FOR THE TREATMENT OF ESOPHAGEAL VARICES

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Abstract : The correlation of between the endoscopic findings of esophageal varices and endoscopic ultrasound findings of the collaterals outside the esophageal wall in patients with portal hypertension remains unclear. We investigated the relationship between esophageal varices and the collaterals by endoscopy and endoscopic ultrasound. Moreover, we investigated the correlation between the collaterals around the esophagus and recurrence of esophageal varices in patients with portal hypertension who had undergone endoscopic injection sclerotherapy. The collaterals were divided into two groups: 1; those with peri-esophageal collateral veins (peri-ECVs) adjacent to the muscularis externa of the esophagus, and 2; those with para-esophageal collateral veins (para-ECVs) distal to the esophageal wall without contact with the muscularis externa. Peri- and para-ECVs were scored as mild or severe according to the stage of development. According to endoscopy, the varix form was significantly larger in severe peri-ECVs group than in mild peri-ECVs group. In contrast, the varix form did not differ significantly between the mild and severe para-ECVs group. The prevalence of perforating veins increased according to the varix form. With regard to variceal recurrence, in patients with variceal recurrences, EUS findings included a significantly higher incidence of severe-type peri-ECVs, a significantly larger number of perforating veins, and a significantly larger diameter of perforating veins compared with patients without recurrence. Moreover, when EUS found the abnormalities when no endoscopic recurrence was found, the results were the almost same as the findings when EUS was performed at the same time when endoscopic recurrence was found. In conclusion, the presence of

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severe peri-ECVs and large perforating veins in the esophageal wall strongly correlates with occurrence and recurrence of esophageal varices in patients with portal hypertension. An understanding of these EUS abnormalities on the basis of hemodynamics around the esophagus is thought to be important for management of esophageal varices in patients with portal hypertension.

Key words : esophageal varices, endoscopic ultrasound

INTRODUCTION

In patients with esophageal varices accompanied by complicating portal hypertension, a large network of portal-systemic collateral veins develops. Frequent and significant pathways of collaterals consist of gastro-esophageal varices and veins outside the esophageal wall extending from the left and short gastric veins¹⁻⁴⁾. Percutaneous transhepatic portography (PTP) has been performed in order to analyze the porto-systemic circulation in patient with portal hypertension, but some vascular structures inside and outside the esophageal wall that serve as collaterals can not be distinguished by PTP. On the other hand, it is possible to clearly distinguish veins inside and outside the esophageal wall by endoscopic ultrasonography. Blood vessels outside the esophageal wall are visualized as low echoic round spaces, which are identified as the azygos vein, hemiazygous vein, para-esophageal veins, and peri-esophageal veins by EUS. EUS can be used to visualize dilated veins outside and adjacent to the esophageal wall as collateral veins in portal hypertension⁵⁻⁹⁾. The recent development of an endoscope attached to an ultrasonic miniprobe (UMP) that has high resolution enables vascular structures to be observed in more detail than that afforded by conventional EUS^{7,8)}. Due to the higher ultrasound frequency of the catheter-based miniature transducer, the resolution of this system is better than that of conventional EUS systems.

Treatment of esophageal varices requires a good outcome with no recurrence. Therefore, understanding the vascular structures of portal-systemic collaterals perforating or running parallel to the esophageal wall may be useful for endoscopic injection sclerotherapy (EIS)^{10,11)} for varices to predict the efficacy and safety of an intravenously injected sclerosant.

We examined collaterals around the esophagus in patients with portal hypertension using EUS with UMP^{12,13)} in order to 1) analyze the vascular structure around the esophagus using UMP so as to clarify the association of this structure with the development of esophageal varices, 2) determine the association of veins around the esophagus with variceal recurrence in patients who had undergone EIS, and 3) determine whether UMP findings can be used to predict variceal recurrence. We herein introduce these our studies in the pages that follow.

ENDOSCOPIC AND ENDOSCOPIC ULTRASONOGRAPHIC FINDINGS
IN PATIENTS WITH ESOPHAGEAL VARICES

Based on the endoscopic findings, the esophageal varix form (F) was classified according to the Japan Society for Portal Hypertension and Esophago-Gastric Varices¹⁴⁾, F1 (straight varix), F2 (enlarged tortuous varix), and F3 (largest varix). In the case where a patient had several varices, the F factor was determined based on the most extensive varix.

The structure of vessels inside and outside the esophageal wall was examined using a 20-MHz UMP (UM-3R, Olympus, Tokyo, Japan) that passed through the biopsy channel of the video endoscope. This system enables a 360° radial scan. Before examination, the esophagus was filled with deaerated water through a water supply tube attached to the fiberscope.

In patients with portal hypertension, many kinds of collaterals around the esophagus were visualized by EUS, especially by using an UMP with high resolution. Schematic representations of the vessels inside and outside the esophageal wall are presented in Fig. 1¹²⁾. Since such vessels were not seen in patients without portal hypertension, the vessels outside the esophageal wall in patients with esophageal varices were considered to be collateral veins.

The esophageal collateral veins (ECVs) outside the esophageal wall detected by using an UMP were divided into two groups according to the location of the veins: peri-ECVs and para-ECVs. Peri-ECVs appeared as smaller vessels adjacent to the muscularis externa of the esophagus as seen in Fig. 2. Para-ECVs appeared as larger vessels distal to the muscularis externa of the esophagus separated by a clear hyper-echoic border as seen in Fig. 3. Peri-ECVs and para-ECVs were scored as

Fig.1 Schematic drawing shows esophageal varices and the vascular structures around the esophageal wall as determined with the 20 MHz ultrasonic micro-probe.

Fig. 2 Endoultrasonographic imaging of the esophagus shows smaller vessels in continuity and adjacent to the muscularis externa (peri-ECVs) (arrows) and esophageal varices (long arrow). These vessels together are designated a venous plexus.

Fig. 3 Endoultrasonographic imaging of esophagus shows several isolated, round shaped vessels separated from the muscularis externa (para-ECVs) (arrow) and esophageal varices (long arrow) are seen.

Fig. 4 Endoultrasonographic imaging of esophagus shows perforating vein (long arrow) between esophageal varices and para-ECVs with a separation of clear hyper-echoic border to the muscularis externa (arrows).

Fig. 5 Endoultrasonographic imaging of esophagus shows several vessels with hypoechoic lumens (arrows) in the esophago-gastric wall at the esophago-gastric junction. These vessels connect with esophageal varices.

mild or severe according to the stage of development. Mild peri-ECVs were defined as fewer than four small vessels with diameters of less than 2 mm adjacent to the esophageal wall, and severe peri-ECVs were defined as five or more small vessels adjacent to the esophageal wall. On the other hand, mild para-ECVs were defined as a few small vessels of less than 5 mm in diameter distal to the esophageal wall of the esophagus separated by a clear hyper-echoic border, and severe para-ECVs were defined as vessels with diameters of more than 5 mm distal to the esophageal wall of the esophagus separated by a clear hyper-echoic border.

Perforating veins are those that have penetrated the esophageal wall and have connected with either peri-ECVs or para-ECVs. UMP images of perforating veins are presented in Fig. 4.

In the esophago-gastric junction (EGJ) region, small vessels of less than 2 mm in diameter with anechoic or hypoechoic lumens were occasionally observed in patients with portal hypertension. UMP images of vessels at the EGJ are presented in Fig. 5.

CORRELATION BETWEEN COLLATERAL VEINS AROUND THE ESOPHAGUS AND ESOPHAGEAL VARICES (TABLE 1¹²⁾)

To determine the correlation between collateral veins around the esophagus before treatment, 22 patients with untreated esophageal varices caused by portal hypertension were studied at the Department of Internal Medicine II of Fukushima Medical University.

The frequencies of peri-ECVs and para-ECVs in the 22 patients with esophageal varices were 18 (81.8%) and 14 (63.6%), respectively. The intensities of the peri-ECVs and para-ECVs in the patients were compared with the intensities of variceal forms in the patients. According to endoscopy, the varix form (F1, F2 and F3) was significantly larger in severe peri-ECVs veins group than in the mild peri-ECVs group ($p < 0.01$). In contrast, the varix form did not differ significantly between the mild and severe para-ECVs veins groups.

Table 1 The correlation between esophageal varices and collateral veins around esophagus

Esophageal varices	Peri-ECVs		Para-ECVs		Perforating veins		
	Mild	Severe [†]	Mild	Severe	No. of patients with findings (%)	Mean number $\pm$ SD	Mean diameter (mm) $\pm$ SD
F1 (7)	7	0	3	4	4 (57.1%)	1.0 $\pm$ 0.0*	1.0 $\pm$ 0.0*
F2 (8)	2	6	3	5	7 (87.5%)	1.86 $\pm$ 0.90 [§]	1.62 $\pm$ 0.77 [§]
F3 (7)	0	7	3	4	7 (100%)	2.14 $\pm$ 0.69* [§]	2.13 $\pm$ 1.26* [§]
Total (22)	9	13	9	13	16 (80%)	1.88 $\pm$ 0.80	1.83 $\pm$ 1.05

[†] : mild versus severe $p < 0.05$

* : F1 versus F3 $p < 0.01$

[§] : F2 versus F3 $p < 0.05$

Perforating veins were detected at the lower esophagus in 18 of 22 patients (81.8%) by ultrasound. The prevalence of perforating veins increased according to the varix form. In the 22 patients examined, a total of 18 perforating veins of both types (peri-ECVs and para-ECVs) were observed at the lower esophagus. The prevalence of perforating veins increased according to the varix form (F); 4 of 7 (57.1%) in F1, 7 of 8 (87.5%) in F2 and all 7 (100%) in F3 grade. When we analyzed the perforating veins on the basis of F factor of the varices, the mean number of perforating veins in each patient increased according to the F factor of the varices (1.0 ± 0.0 in F1 and 2.14 ± 0.69 in F3; $p < 0.01$). Similarly, the mean diameter of the perforating veins increased from 1.0 ± 0.0 mm in F1 and 2.13 ± 1.26 mm in F3 grade ($p < 0.01$). Using Doppler endoscopic ultrasonography, the presence of perforating veins as afferent veins to esophageal varices was observed^{15,16}. Our preliminary study using color Doppler endoscopic ultrasonography (CDEUS) also showed that the perforating veins in 87.5% of patients with varices were afferent. Thus, it is possible that perforating veins are associated with the development of esophageal varices.

Veins at the EGJ were detected using an UMP in all cases. These veins are thought to be associated with variceal occurrence in patients with portal hypertension.

ASSOCIATION OF COLLATERALS AROUND THE ESOPHAGEAL WALL WITH VARICEAL RECURRENCE AFTER TREATMENT (TABLE 2¹³)

To treat the esophageal varices, EIS was performed using a flexible gastrointestinal endoscope and combination of intravariceal injection of 5% ethanolamine oleate (EO) and extravariceal injection of 1% aethoxysclerol (AS), as described previously^{10,11,17,18}. This procedure was repeated once a week for 4 to 6 times until all varices had been completely eradicated.

On the basis of the results of endosonographic analysis of collateral veins in patients with portal hypertension, we investigated the correlation between the size of collaterals, including perforating veins and veins at the EGJ, and endoscopic recurrence of esophageal varices in patients with portal hypertension who had undergone endoscopic injection sclerotherapy. Thirty-eight patients who had undergone endoscopic injection sclerotherapy were examined every 3 to 4 months by endoscopy and an UMP for a period of 2 years. Recurrence of esophageal varices was determined by endoscopic findings of either new varix formation or appearance of red color sign.

Ten of the 38 patients (26.3%) showed endoscopic recurrence at a mean duration of 10.9 months after EIS. In patients with variceal recurrences, EUS findings included a significantly ($p < 0.001$) higher incidence of severe peri-ECVs, a significantly ($p < 0.001$) larger number of perforating veins, and a significantly ($p < 0.001$) larger diameter of perforating veins compared with patients without recurrence (8 of 10,

Table 2 A comparison of UMP images when endoscopic variceal recurrence was found between the recurrence group and the non-recurrence group

UMP findings	recurrence group <i>n</i> =10	no recurrence group <i>n</i> =28	<i>p</i> value
Mean duration from the end of EIS until UMP examination			
mean±SD (range) month	10.9±5.1 (6-20)	11.3±1.0 (10-14)	ns
peri-ECVs			
Severe (2 mm or more)	8 (80%)	2 (7.1%)	} <i>p</i> < 0.001
Mild (less than 2 mm) (in diameter)	2 (20%)	26 (92.9%)	
para-ECVs			
Severe (5 mm or more)	6 (60%)	12 (42.9%)	} ns
Mild (less than 5 mm) (in diameter)	4 (40%)	16 (57.1%)	
perforating veins			
number : mean±SD (range)	9 (90%) 1.30±0.67	6 (21.4%) 0.21±0.42	<i>p</i> < 0.001
maximum diameter : mean±SD (range) mm	2.00±1.15	0.32±0.67	<i>p</i> < 0.001
type of perforating veins connecting with			
severe peri-ECVs	8	0	} <i>p</i> < 0.005
mild peri-ECVs	0	4	
severe para-ECVs	3	2	} unevaluated
mild para-ECVs	0	0	
veins at EGJ	5 (50%)	8 (28.6%)	ns

UMP: ultrasound mini-probe

ECVs: esophageal collateral veins

EGJ: esophago-gastric junction

80% vs. 2 of 28, 7.1%, 1.30 vs. 0.21; 2.00 mm vs. 0.32 mm, respectively). The presence of veins at the EGJ was not correlated with the recurrence of esophageal varices. These results suggested that severe-type peri-ECVs and large perforating veins of the esophagus detected by EUS in patients treated by all session of EIS are significantly indicative of the recurrence of esophageal varices.

PREDICTION OF VARICEAL RECURRENCE AFTER TREATMENT USING EUS (TABLE 3¹³⁾)

To evaluate the usefulness of EUS for patients with portal hypertension who have undergone EIS, we retrospectively studied whether EUS findings could be used to predict variceal recurrence. We compared preceding UMP images in the recurrence and non-recurrence groups when endoscopic variceal recurrence was found. The mean duration from the end of treatment until evaluated UMP examination was matched between the two groups.

Table 3 A comparison of the preceding UMP images when endoscopic variceal recurrence was found between the recurrence group and the non-recurrence group

UMP findings	recurrence group <i>n</i> = 10	no recurrence group <i>n</i> = 28	<i>p</i> value
Mean duration from the end of EIS until UMP examination			
mean±SD (range) month	8.0±4.4 (3-16)	8.1±1.0 (7-10)	ns
peri-ECVs			
Severe (2 mm or more)	7 (70%)	1 (3.6%)	} <i>p</i> < 0.001
Mild (less than 2 mm) (in diameter)	3 (30%)	27 (96.4%)	
para-ECVs			
Severe (5 mm or more)	5 (50%)	9 (32.1%)	} ns
Mild (less than 5 mm) (in diameter)	5 (50%)	19 (67.9%)	
perforating veins			
number : mean±SD (range)	9 (90%) 1.10±0.57	6 (21.4%) 0.19±0.39	<i>p</i> < 0.001
maximum diameter : mean±SD (range) mm	1.50±0.71	0.29±0.66	<i>p</i> < 0.001
type of perforating veins connecting with			
severe peri-ECVs	7	0	} <i>p</i> < 0.005
mild peri-ECVs	1	4	
severe para-ECVs	2	1	} unevaluated
mild para-ECVs	0	0	
veins at EGJ	5 (50%)	8 (28.6%)	ns

UMP: ultrasound mini-probe

ECVs: esophageal collateral veins

EGJ: esophago-gastric junction

The results were almost the same as those when UMP examination was performed on the same day when endoscopic recurrence was found. Severe peri-ECVs were significantly (*p* < 0.001) more frequent in the recurrence group (7 of 10, 70%) than in the non-recurrence group (1 of 27, 3.6%). The frequency, the mean number and the maximum diameter of the perforating veins were significantly (*p* < 0.001) higher in the recurrence group (90%, 1.10±0.57, 1.50±0.71 mm, respectively) than in the non-recurrence group (21.4%, 0.19±0.39, 0.29±0.66 mm, respectively). The maximum diameter of the perforating veins ranged from 1 mm to 2 mm. The perforating veins tended to be thinner than those on the same day as that when endoscopic recurrence was found. The frequency at which veins were found at EGJ was the same when UMP images obtained at the preceding examination were compared with UMP images obtained when endoscopic recurrence was found as the findings on the same day when endoscopic recurrence was found.

USEFULNESS OF ENDOSCOPIC ULTRASONOGRAPHIC ANALYSIS OF VARICEAL HEMODYNAMICS FOR THE TREATMENT OF ESOPHAGEAL VARICES

We could adequately visualize and evaluate the venous morphology outside the lower esophageal wall in patients with esophageal varices using EUS. We demonstrated that severe peri-ECVs and large perforating veins play an important role in development of esophageal varices in untreated patients with portal hypertension. We also analyzed the characteristics of the ECVs, perforating veins, and veins at the EGJ by EUS in connection with the recurrence of esophageal varices after EIS. Vessels feeding the esophageal varices have been recognized to be important for recurrence after EIS as well as occurrence of esophageal varices before EIS in patients with portal hypertension. Soderlund *et al.*¹⁹⁾ reported that selective elimination of submucosal varices without embolization of the periesophageal and paraesophageal collaterals resulted in a higher recurrence rate of varices. The results of our investigation and those previous studies have shown that detection of peri-ECVs by EUS with UMP and perforating veins and treatment of them by EIS appears to be important for the treatment of esophageal varices. The disappearance of peri-ECVs by EIS in which a sclerosant is poured through perforating veins connecting with the varices is essential for reducing the recurrence rate of esophageal varices. With regard to para-ECVs, in cases in which para-ECVs are connected with esophageal varices via perforating veins, the disappearance of para-ECVs also appears to be important for preventing the inflow of venous blood to the varices.

To prevent variceal recurrence, mucosal fibrosing using aethoxysclerol (AS)¹¹⁾ or Laser²⁰⁾, a kind of EIS, has widely been performed in Japan. If EUS abnormalities are associated with variceal recurrence, we recommend the use of the mucosal fibrosing method. On the other hand, if peri-ECVs and perforating veins are not detected before treatment, it is considered that mucosal fibrosing method will not be performed. In addition, there are several reports on the benefit of the addition of a beta-blocker, such as propranolol, to EIS^{21),22)}. Bosch *et al.*²³⁾ reported that propranolol consistently and markedly reduces the blood flow in collaterals around the esophagus, such as the azygos vein. If recurrence-related abnormalities are visualized by EUS after EIS, administration of a beta-blocker is recommended.

In conclusion, the presence of severe peri-ECVs and large perforating veins in the esophageal wall strongly correlates with occurrence and recurrence of esophageal varices in patients with portal hypertension. An understanding of these EUS abnormalities on the basis of hemodynamics around the esophagus is thought to be important for management of esophageal varices in patients with portal hypertension.

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