Portal Hypertensive Enteropathy in Liver Cirrhosis

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ABSTRACT

***Background/Aim**: Some studies found that portal hypertension cause complication such as portal hypertensive gastroenterocolopathy. This study was done to find any abnormalities in the small intestinal mucosa and villi of the portal hypertensive patients.*

***Method**: Thirty patients with liver cirrhosis, portal hypertension and esophageal varices between 2000 - 2001 were included in this study. A duodenoscopic examination was performed to determine any abnormalities. Biopsy specimens were taken from the descending part of duodenum and the duodenal bulb for histopathological examination. The findings were compared to 37 functional dyspepsia patients.*

***Result**: In the duodenal bulb and descending part of duodenum: the width of the villous of the portal hypertensive group was larger than the control ($p < 0.001$), the diameter of the mucosal villous vessel was larger than in the control ($p < 0.001$) and the thickness of the mucosal villous vessel wall was thicker than in the control ($p < 0.001$).*

***Conclusion**: There were abnormalities of the mucosa in portal hypertensive enteropathy patients including the mucosal vessel diameter, wall thickness, number of goblet cells.*

***Keywords**: portal hypertensive enteropathy, liver cirrhosis*

INTRODUCTION

Studies have found that portal hypertension may cause gastrointestinal complications like esophageal varices, gastric varices, portal hypertensive gastroenterocolopathy, hemorrhoids, etc.[1-16] Portal hypertensive enteropathy could cause gastrointestinal symptoms including chronic diarrhea, bleeding, Small Intestine Bacterial Overgrowth (SIBO).[1-16,17,18]

Some studies found that the capillary vessels of the small intestinal mucosa had a wider diameter and that the wall was thicker than normal.[1,3,19] This study was conducted to uncover any abnormalities in the small intestinal mucosa and villi of portal hypertensive patients.

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METHODS

Thirty patients with cirrhosis of the liver and portal hypertension and esophageal varices who came to the clinic between 2000 and 2001 were included in this study. The patients were seen as in and out patients of the Division of Gastroenterology and Hepatology Department of Internal Medicine Cipto Mangunkusumo hospital, Indonesia. A duodenoscopic examination was performed on each of the patients to determine any abnormalities. Blood coagulation tests were performed before duodenoscopy. We used the Olympus PCF-10 pediatric colonoscope for the examination. Biopsy

specimens were taken from the descending part of the duodenum (2 specimens) and the duodenal bulb (2 specimens), and histopathological examination was performed. Patients were excluded if they were uncooperative, had no esophageal varices, the blood coagulation result exceeded 2 x normal, had DIC and other hemostatic abnormalities, or had active bleeding.

The diagnosis of liver cirrhosis will be supported by ultrasonography examination. The liver function was graded as A, B and C according to Child-Pugh criteria (table 1).[20]

Table 1. Child Pugh criteria

Variable	1	2	3
Ascites	No	Mild	Severe
Encephalopathy	No	1-2	3- 4
Total bilirubin (mg/dL)	< 2	2- 3	> 3
Serum albumin (g/dL)	> 3.5	2.8- 3.5	< 2.8
Prothrombin time (sec)	< 16	17 - 21	> 22
Total Pugh Score	Child class		
< 6	A		
7 - 9	B		
10 – 15	C		

Cited from Pugh RNH, et al. Br J Surg 1973.[20]

The endoscopical appearances of gastric mucosa in portal hypertensive gastropathy was graded according to the OMED and Indonesian grading system. The grade of portal hypertensive gastropathy was mild, moderate and severe. Mild if we found mosaic pattern appearance, mild hyperemia, and small vascular lesions (small red color sign or red dot) less than 10. Moderate if we found mosaic pattern appearance, moderate hyperemia, and 10-20 small vascular lesions. Severe if we found mosaic pattern appearance, severe hyperemia, more than 20 small vascular lesions, cherry red spots, black brown spots and ulcer.[21-24] The endoscopical appearances of duodenal mucosa in portal hypertensive enteropathy was graded according to the Indonesian grading system. The grade of portal hypertensive enteropathy was mild, moderate and severe. Mild if we found mild hyperemia, and less than 10 small vascular lesions (small red color sign or red dot). Moderate if we found moderate hyperemia, and 10-20 small vascular lesions. Severe if we found severe hyperemia, more than 20 small vascular lesions, cherry red spots, black brown spots and ulcer. Hyperemia if there was an increased vascularity with red mucosa.[23] Vascular lesion (angiectasia) was a red structure of different small sizes and shapes-point, claw, spider, cobweb-due to vascular malformation. It can be single or multiple. Mosaic pattern appearance was multiple erythematous areas outlined by a white reticular network. Cherry red spots were confluent areas of diffuse bleeding. Black brown spots were diffuse dark points and spots due to subepithelial hematin deposits. Ulcer implies a benign defect of the gastro intestinal mucosa, which is larger and deeper than erosion.

The esophageal varices were graded into grade I-IV according to the OMED criteria, in a maximally relaxed esophagus.[23] Grade 1 if there was hardly noticeable protrusion, visible with a valsalva maneuver. Grade 2 if the protrusion of varices was up to 1/4 of the esophageal lumen. Grade 3 if the protrusion of varices was up to 1/2 of the esophageal lumen. Grade 4 if the protrusion of varices was greater than 1/2 of the esophageal lumen.

On histopathology, we counted the maximum diameter of the vessel and thickness of vessel wall in duodeno-jejunal villi, the height, width of the villous mucosa and the intervillous space of the duodeno-jejunal villi. The findings were then compared to the data of 37 functional dyspepsia patients without upper gastrointestinal abnormality (endoscopy and histopathology). The measurements of the mucosa were performed with micrometer and microscope with objective 10 x 10, 10 x 40 and 10 x 100. In magnifying 10 x 10 : 1 U = 10 micrometer and 10 x 40 : 1U = 2.5 micrometer. Haematoxyllin-Eosin was used for the histopathological staining. A scoring system for inflammatory cells (lymphocytes, plasma cells, eosinophils and polymorphonuclear cells) was used as follows: 0 (negative), +, ++ +++. + if the histology showed that the distance between 2 cells was larger than the diameter of the cells. ++ if the histology showed that the distance between 2 inflammatory cells was smaller than the diameter of the cells. +++ if the inflammatory cells were touching each other. The number of goblet cells in 100 mm were measured in all specimens. The data were analyzed with ANOVA and Chi-square/Fischer tests.

RESULTS

The most frequent characteristics of the patients were age 50.55 ± 11.62 years old, male (62.5%), Child C functional status (55.0%), dyspepsia symptom (47.5%), grade III esophageal varices (50%). Diarrhea was seen in two patients (table 2).

We found 100% abnormalities in the stomach which we called portal hypertensive gastropathy. The portal hypertensive enteropathy was found in the duodenal bulb (24 of 40 patients/60%) and in the descending part of duodenum (23 of 40 patients 57.5%) (table 3).

From the histopathological examination in the duodenal bulb, we found that the diameter and wall thickness of the mucosal villi vessels were larger in the portal hypertension group than in the control group ($p < 0.001$) (table 4).

Table 2. Characteristics of the portal hypertensive patients

Characteristics	Frequency (n = 40)	Percent (%)
Mean age (years old)	50.55 ± 11.62	
Sex		
Male : female	25:15	62.5 : 37.5
Child		
A	4	10.0
B	14	35.0
C	22	55.0
Symptom		
Dyspepsia	19/40	47.5
Diarrhea	2/40	5
Diarrhea		
Stool form: soft nonbloody-non steatorrhea	1	
watery	1	
Duration: 4 weeks	1	
7 weeks	1	
Grade of esophageal varices		
I	1	2.5
II	8	20.0
III	20	50.0
IV	11	27.5

Table 3. Endoscopical appearances of portal hypertensive gastro-duodenopathy

Location of abnormality	Grade of hyperemia		Grade of vascular lesion/ red color sign		Ulcer (Yes/No)	Mozaic pattern (Yes/No)	Overall grade of gastro-duodenopathy	
Stomach	Normal	0	Normal	0	No 37	No 0	Normal	0
	Mild	2	Mild	3	Yes 3	Yes 40	Mild	2
	Mod	35	Mod	34			Mod	35
	Severe	3	Severe	3			Severe	3
Duodenal bulb	Normal	16	Normal	17	No 33	No 40	Normal	16
	Mild	14	Mild	13	Yes 7	Yes 0	Mild	12
	Mod	10	Mod	10			Mod	5
	Severe	0	Severe	0			Severe	7
Pars descendens duodenum	Normal	18	Normal	21	No 36	No 40	Normal	17
	Mild	13	Mild	11	Yes 4	Yes 0	Mild	12
	Mod	8	Mod	8			Mod	6
	Severe	1	Severe	0			Severe	5

Table 4. Histopathologic mucosal measurement in the duodenal bulb of the patients

Mucosal measurement (means)	Portal hypertension	Control	p value
Villous height (μm)	266.81 ± 69.16	265.00 ± 81.89	ns*
Crypt height (μm)	221.18 ± 65.23	196.67 ± 56.01	ns*
Villous width (μm)	132.5 ± 36.71	96.00 ± 27.46	< 0.001*
Intervillous space (μm)	47.87 ± 24.30	59.14 ± 74.14	ns*
Crypt: villous ratio	0.86 ± 0.29	0.80 ± 0.26	ns*
Goblet cells in 100 (μm) villous height	3.73 ± 1.32	2.95 ± 1.41	0.026*
Vessels in the top of the villi			
▪ Diameter (μm)	26.31 ± 11.71	12.35 ± 4.73	< 0.001*
▪ Wall thickness (μm)	2.26 ± 0.60	0.81 ± 0.36	< 0.001*
Vessels in the base of the villi			
▪ Diameter (μm)	22.12 ± 10.18	14.07 ± 7.22	< 0.001*
▪ Wall thickness (μm)	2.07 ± 0.54	0.76 ± 0.39	< 0.001*

*Anova/Kruskal Wallis test; ns = not significant

Table 5. Histopathologic mucosal measurement in descending part of duodenum of the patients

Mucosal measurement (means)	Portal hypertension (n = 40)	Control (n = 37)	p value
Villous height (μm)	266.62 ± 64,93	317.27 ± 99.66	0.018*
Crypt height (μm)	209.16 ± 65.52	218.79 ± 84.66	ns*
Villous width (μm)	122.56 ± 39.53	125.76 ± 35.88	ns*
Intervillous space (μm)	37.68 ± 19.84	30.91 ± 34.58	ns*
Crypt: villous ratio	0.81 ± 0.28	0.74 ± 0.34	ns*
Goblet cells in 100 (μm) villous height	4.10 ± 1.74	3.80 ± 2.01	ns*
Vessels in the top of the villi			
▪ Diameter (μm)	26.43 ± 9.37	12.29 ± 5.63	< 0.001*
▪ Wall thickness (μm)	2.20 ± 0.42	0.56 ± 0.19	< 0.001*
Vessels in the base of the villi			
▪ Diameter (μm)	26.18 ± 16.94	13.58 ± 5.88	< 0.001*
▪ Wall thickness (μm)	2.26 ± 0.45	0.71 ± 0.31	< 0.001*

*Anova/Kruskal Wallis test; ns = not significant

Table 6. Other abnormalities in histopathology

Histopathology		Portal hypertensive enteropathy group (n = 40)	Control group (n = 37)	p value
Duodenal bulb				
Lymphocyte	+	24	8	< 0.001*
	++	16	29	
Plasma cell	0	0	0	ns*
	+	40	37	
Eosinophil	0	0	3	< 0.001*
	+	39	12	
	++	1	22	
Polymorphonuclear cell	0	20	3	< 0.001*
	+	20	34	
Stage of inflammation	0	0	0	0.003*
	+	24	9	
	++	16	28	
Descending part of duodenum				
Lymphocyte	+	25	36	< 0.001*
	++	15	1	
Plasma cell	0	0	1	ns*
	+	40	36	
Eosinophil	0	18	15	ns*
	+	22	22	
Polymorphonuclear cell	0	26	33	0.012*
	+	14	4	
Stage of inflammation	+	25	36	< 0.001*
	++	15	1	

*Chi-square/fisher test; ns = not significant

From histopathological examinations in the descending part of duodenum, we found that the diameter and wall thickness of the mucosal villi vessels were larger in the portal hypertension group than in the control group ($p < 0.001$) (table 5).

In the duodenal bulb, the lymphocyte infiltration, polymorphonuclear cell infiltration and stage of inflammation were more prominent in the control group than in the portal hypertension group. In the descending part of duodenum, the lymphocyte infiltration,polymorphonuclear cell infiltration and stage of inflammation were more prominent (increased) in the portal hypertension group than in the control group (table 6).

DISCUSSION

The mean age of portal hypertension patients in this study (50.55 ± 11.62) was the same as in another study in portal hypertensive gastropathy patients.[6] Most patients in this study were male, the same as in the other study.[6]

There were 47.5% of the portal hypertension patients complaining of dyspepsia and 5% had chronic diarrhea. These symptoms were different from those found in other studies.[6,7]

Child C function status was the most frequent finding in this study. This was the same as in other studies.[6,7] Two patients were complaining of chronic diarhea, this symptom could be due to small intestinal bacterial overgrowth, intestine mucosal abnormalities due to portal hypertension, maldigestion, etc.[18,25,26]

Portal hypertension diffusely affects the gastrointestinal tract. It has been reported that besides the stomach, the mucosa of the intestine and the colon is also affected.[26] A lot of studies revealed the close correlation between the occurrence of enterocolopathy and portal hypertension gastropathy.[8-16] These results were the same as the result of this study, which revealed the occurrence of portal hypertension gastropathy in 100% patients, enteropathy in the duodenal bulb in 24 from 40 (60%) patients and enteropathy in the pars descendens duodenum in 23 from 40 (57.5%) patients.

The histopathologic examination of the duodenal bulb revealed that the villous width in the portal hypertension group was greater than in the control group. This finding was inline with other studies.[1-3,11,14,15] The diameter and wall thickness of mucosa villous vessels of the duodenal bulb and descending part of duodenum in the portal hypertension group were greater than in the control group. These findings were the same as in other studies.[1-3,11,14,15]

The histopathologic examination of the descending part of duodenum revealed that the villous height in the portal hypertension group was shorter than in the normal group. This was still questionable and could be due to some error or other factors.

The goblet cell number in 100 mm villous height in the duodenal bulb was higher in the portal hypertension group than in the control group. This finding was the same as the finding of goblet cells in alcoholic patients, which revealed an increase of goblet cells.[27] This abnormality could be due to local adaptation of the small intestine mucosa to pathologic irritation, portal congestion or other factors.

The lymphocyte infiltration, stage of inflammation and polymorphonuclear cell infiltration in the pars descendens duodenum were more prominent in the portal hypertension group than in the control group. These findings could not be compared, because there were no other studies on inflammatory cells in portal hypertensive enteropathy. However, there was a histological study in portal hypertensive colopathy, which showed evidence of chronic or acute nonspecific inflammation[26] and another study in duodenal mucosa in rats with portal hypertension showed an increase in mast cells density compared to controls.[14] All these abnormalities could be caused by the longstandingcongestion or engorgement in the portal system in portal hypertension.

These findings were not the same as the result in the duodenal bulb, where we found the opposite, the lymphocyte infiltration, stage of inflammation and polymorphonuclear cells infiltration was more prominent in the control group compared to the portal hypertension group. This result needs further study.

CONCLUSION

We have found abnormalities in the mucosa in portal hypertensive enteropathy patients including the mucosal vessel diameter, wall thickness, goblet cells, lymphocyte infiltration, and polymorphonuclear cells.

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