Histomorphometric Study of Portal Hypertensive Enteropathy

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Histopathologic features of duodenal and jejunal mucosal biopsy specimens obtained from 58 patients with portal hypertension and 30 healthy volunteers were studied. Dilated mucosal vessels with thickened walls were seen in duodenal and jejunal biopsy specimens from 39 (67%) and 41 (71%) of the patients, respectively, compared with corresponding biopsy specimens from 8 (27%) and 6 (2%) of the control subjects. The difference between the two groups was statistically significant. Other important histologic features in the patient group included edema of the lamina propria, fibromuscular proliferation, a decreased villous/crypt ratio, and thickened muscularis mucosae. The mean ± SD thickness of capillary wall and diameter were significantly more in the patient group compared with those in the control subjects. We conclude that thick-walled dilated vessels along with edema of the lamina propria, fibromuscular proliferation, a decreased villous/crypt ratio, and thickened muscularis mucosae form a characteristic picture of portal hypertensive enteropathy. These changes seem to be a part of the changes seen in the gastrointestinal tract of patients with portal hypertension without any meaningful clinical implication except the increased chance of occult gastrointestinal blood loss. (Key words: Cirrhosis; Enteropathy; Liver; Histology) Am J Clin Pathol 1997;108:652–657.

Endoscopic and histologic changes in the gastric mucosa of patients with portal hypertension were first studied by McCormack et al,[1] who labeled them *congestive gastropathy*. Although the endoscopic features of the gut mucosa have been studied in detail,[2–6] the histologic changes are still confusing and lack distinct diagnostic criteria.[5,7,8] Furthermore, small intestinal mucosal changes have not been studied in detail, and only a few studies, on a limited number of patients, have been reported.[1,9] This study was therefore undertaken to study the histologic changes in the duodenal and jejunal mucosal biopsy specimens from patients with portal hypertension.

MATERIALS AND METHODS

Fifty-eight patients with cirrhosis of liver and 30 healthy volunteers were studied. Written informed consent was obtained from all subjects.

The diagnosis of cirrhosis was made by biopsy of the liver in patients who did not have coagulopathy and on the basis of the clinical features, a hepatic function profile, ultrasonographic examination of the abdomen, ascitic fluid examination, and upper gastrointestinal endoscopy in those who had coagulopathy. In addition, postmortem biopsy specimens were obtained for all patients with coagulopathy at the time of death. The cause of cirrhosis was determined on the basis of the clinical history, serologic studies, and the findings from the biopsy of the liver.

All subjects underwent upper gastrointestinal endoscopy using a pediatric colonoscope (CF-P 20L, Olympus, Tokyo, Japan). During endoscopy, the presence and grade of esophageal varices and gastric varices and the evidence of portal hypertensive gastropathy were recorded.

The grade of esophageal varices was given according to Conn[10] as follows: grade 1, small varices only detectable by performing the Valsalva maneuver; grade 2, small varices (approximately 1 to 3 mm in diameter) visible without performing the Valsalva maneuver; grade 3, moderate-sized varices (3 to 6 mm in diameter); and grade 4, large varices (greater than 6 mm in diameter).

The severity of cirrhosis was classified according to the Child-Pugh score.[11] Briefly, five parameters, serum bilirubin, ascites, encephalopathy, serum albumin, and prothrombin time, were evaluated. Each parameter

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TABLE 1. CHILD-PUGH CLASSIFICATION OF THE SEVERITY OF HEPATIC DISEASE

Variable	*Points*		
	1	*2*	*3*
Grade of encephalopathy	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/100 mL)	1–2	2–3	> 3
Serum albumin (mg/mL)	3.5	2.8–3.5	< 2.8
Prothrombin time (seconds, prolonged)	1–4	4–6	> 6

was given a score of 1 to 3 as shown in Table 1. Patients with a total score of up to 6 were considered to have Child-Pugh class A disease, those with a score of 7 to 9, Child-Pugh class B disease, and those with a score of 10 or more, Child-Pugh class C disease.

The changes of portal hypertensive gastropathy were classified according to the criteria given by McCormack et al.[1] A fine pink speckling or scarlatina rash, superficial erythema on the surface of the gastric rugae giving a striped appearance, or a snakeskin appearance or "mosaic pattern" were classified as mild changes. Severe changes were denoted by the presence of discrete cherry-red spots and by the presence of diffuse hemorrhagic gastritis.

After thorough endoscopic examination, two endoscopic biopsy specimens were taken from the fundus and antrum of the stomach and duodenum. Jejunal biopsy specimens were obtained by pushing the biopsy forceps as far as possible. All the biopsy specimens were processed routinely and were stained with hematoxylin and eosin, van Gieson's stain, and periodic acid–Schiff stain. All the histologic sections were examined by two pathologists who were unaware of the clinical details, the diagnosis, or the endoscopic findings.

Sections from duodenal and jejunal biopsy specimens were examined for the severity and type of cellular infiltrate in the mucosa, edema of the lamina propria, fibromuscular proliferation, the villous/crypt ratio, and the thickness of the muscularis mucosae. Mucosal vascular changes (ie, in venules and capillaries) were studied in detail with special reference to an increase in the diameter, the presence or absence of red blood cells in the lumen of vessels, and an increase in thickness of the vessel wall. The changes in the vessels were divided into two groups as follows:

1. Dilated (increase in the diameter) and congested (red blood cells present in the lumen) irrespective of the vessel wall thickness.

2. Dilated and thick-walled irrespective of the presence or absence of red blood cells in the lumen.

All of the histologic variables were simply observed as to presence or absence and were not scored. A decreased villous/crypt ratio was considered less than 3:1.

Morphometry

The maximum diameter of the capillaries and the maximum thickness of the capillary walls were measured in five consecutive villi per section in the first, third, and fifth serial sections of each biopsy specimen with the help of a Leitz optical micrometer (Ernest Leitz, Wetzlar, Germany). The mean of these values was used for statistical calculations.

Statistics

Statistical calculations were performed using the Student's t test and the χ^2 test with or without Yates' correction, as appropriate. The value at .05 was set as the critical level of significance.

RESULTS

Control Subjects

There were 23 men and 7 women in this group. The mean age ± SD was 33 $^1/_2$ ± 14 years (range, 18–70 years). None of the subjects in this group had esophageal varices, gastric varices, or portal hypertensive gastropathy.

Patients

There were 42 men and 16 women in this group. The mean age ± SD was 39 ± 16.0 years (range, 24–75 years). The difference from the control group was not statistically significant. Cirrhosis was due to a virus in 54 patients and to alcoholism in 4 patients.

TABLE 2. HISTOMORPHOMETRIC VARIABLES OF DUODENAL BIOPSY SPECIMENS IN CONTROL SUBJECTS AND PATIENTS WITH PORTAL HYPERTENSION*

Variable	*Patients (n = 58)*	*Control Subjects (n = 30)*	P
Dilated and congested vessels	37 (64)	25 (83)	< .10
Dilated vessels with thick walls	39 (67)	8 (27)	< .001
Inflammation	15 (26)	6 (20)	> .50
Edema of lamina propria	24 (41)	4 (13)	< .001
Fibromuscular proliferation in lamina propria	21 (36)	4 (13)	< .01
Decreased villous/crypt ratio	17 (29)	2 (7)	< .05
Thickened muscularis mucosae	41 (71)	14 (47)	< .001
Mean ± SD thickness of capillary wall (μm)	6.0 ± 1.9	2.9 ± 1.0	< .001
Mean ± SD diameter of the capillaries (μm)	66.0 ± 13.0	46.0 ± 10.0	< .05

*Data are given as number (percentage) unless otherwise noted.

TABLE 3. HISTOMORPHOMETRIC VARIABLES OF JEJUNAL BIOPSY SPECIMENS IN CONTROL SUBJECTS AND PATIENTS WITH PORTAL HYPERTENSION

Variable	*Patients (n = 58)*	*Control Subjects (n = 30)*	P
Dilated and congested vessels	37 (64)	24 (80)	< .50
Dilated vessels with thick walls	41 (71)	6 (20)	< .001
Inflammation	17 (29)	7 (23)	> .50
Edema of lamina propria	29 (50)	7 (23)	< .001
Fibromuscular proliferation in lamina propria	28 (48)	5 (17)	< .001
Decreased villous/crypt ratio	22 (38)	5 (17)	< .05
Thickened muscularis mucosae	40 (69)	12 (40)	< .01
Mean ± SD thickness of capillary wall (μm)	5.8 ± 2.2	2.9 ± 1.1	< .001
Mean ± SD diameter of the capillaries (μm)	69.0 ± 14.0	46.0 ± 11.0	< .05

*Data are given as number (percentage) unless otherwise noted.

All patients had esophageal varices. Gastric varices were present in 10 patients (17%), portal hypertensive gastropathy was seen in 27 patients (46%) and was mild in all the cases. Duodenal hyperemia was present in 10 patients (17%).

Histologic Findings

Histologic findings are given in Tables 2 and 3. Dilated and congested duodenal vessels were seen in 64% of patients and 83% of the control subjects. The difference was not statistically significant (see Table 2). Similarly, no difference was observed in the number of patients with dilated and congested jejunal vessels compared with the control group (64% *vs* 80%, $P < .50$; see Table 3; Fig 1). A significantly higher number of patients had evidence of thickening of the vascular walls in the biopsy specimens from both sites compared with the control subjects ($P < .001$; see Tables 2 and 3). The thickening, whenever observed, was irregular (Fig 2). Duodenal biopsy specimens from 14 patients (24%) and jejunal biopsy specimens from 17 patients (29%) had thick-walled dilated vessels without red blood cells in their lumen (Fig 3). None of the control subjects had evidence of such changes in the biopsy specimens.

In the duodenum, the frequency of edema of the lamina propria, a decreased villous/crypt ratio, fibromuscular hyperplasia, and thickened muscularis mucosae was significantly different between the patients and the control subjects (see Table 2). In the jejunum, the frequency of edema of the lamina propria, a decreased villous/crypt ratio (Fig 4), fibromuscular hyperplasia, and thickened muscularis mucosae (Fig 5) was significantly different between the two groups (see Table 3).

The inflammatory infiltrate consisted predominantly of mononuclear cells. It was observed in more patients than control subjects, but the difference was not significant for the duodenum or jejunum (see Tables 2 and 3). All variables except inflammation were more frequently observed in sections with predominant thick-walled mucosal vessels than sections with dilated and congested vessels without thickening of vascular walls.

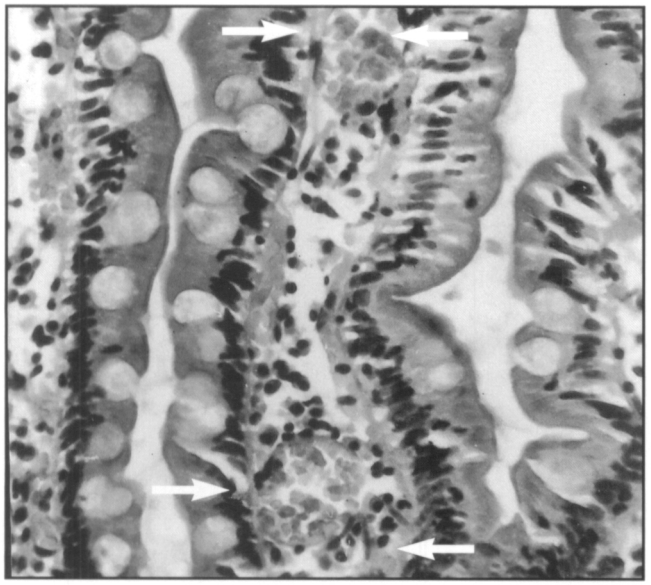

FIG 1. Jejunal villi from a control subject. Note the presence of dilated capillaries full of red blood cells (arrows) (hematoxylin-eosin, ×320).

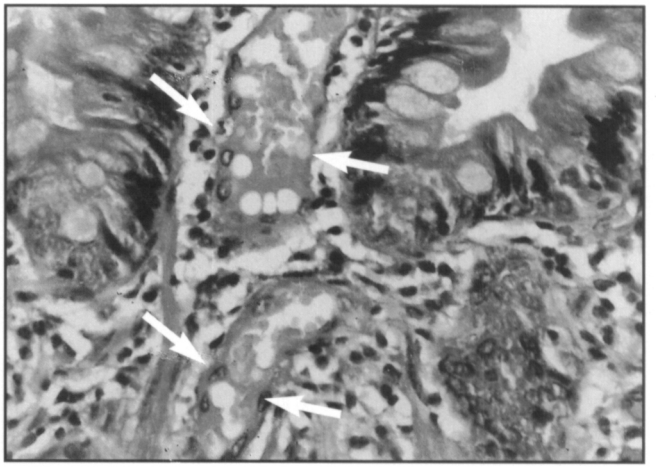

FIG 2. Jejunal biopsy specimen from a patient with portal hypertension. Irregular thickening of the capillary wall (arrows) is evident. Red blood cells can be seen in the lumen of the capillaries (hematoxylin-eosin, ×320).

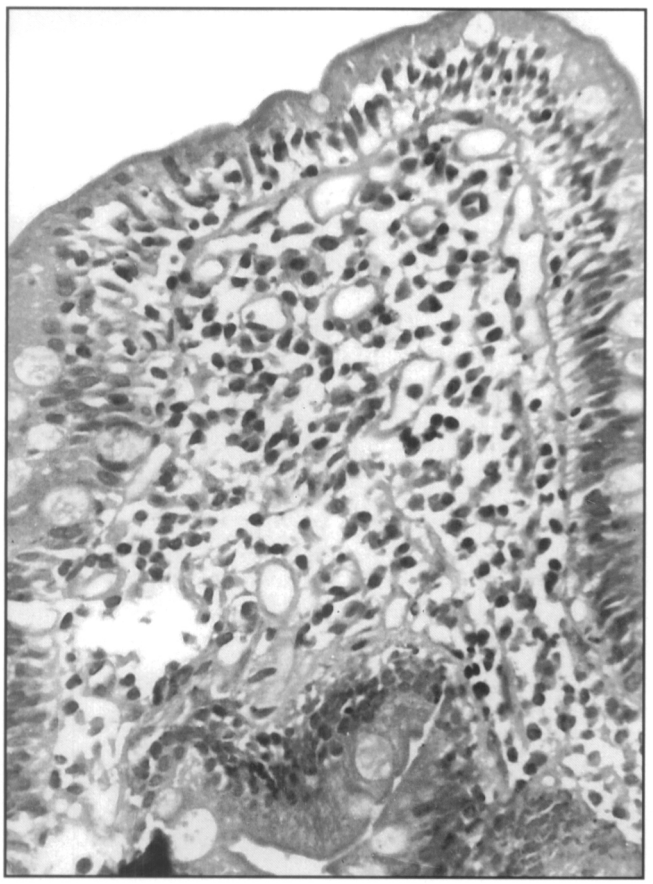

FIG 3. Jejunal villi from a patient with portal hypertension showing thick-walled empty capillaries. The lumen of the capillaries is devoid of red blood cells (hematoxylin-eosin, ×320).

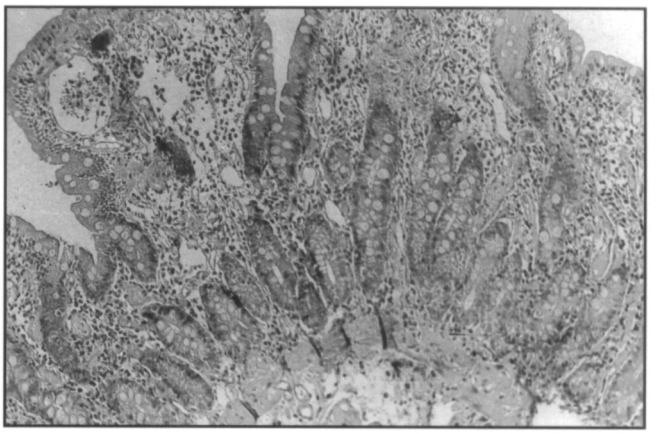

FIG 4. Jejunal biopsy specimen from a patient with portal hypertension. Note the presence of flattened villi leading to a decreased villous/crypt ratio (hematoxylin-eosin, ×80).

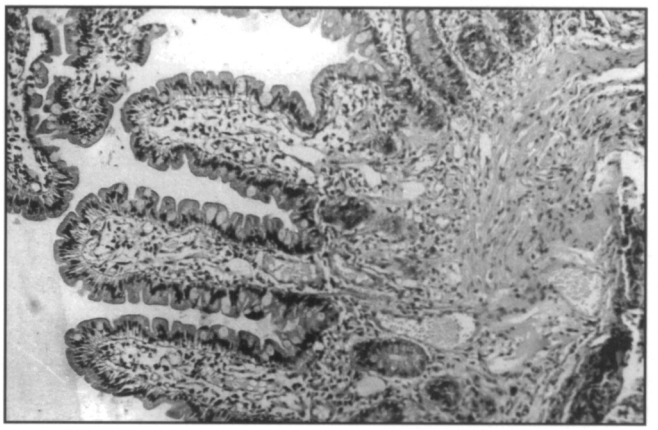

FIG 5. Jejunal biopsy specimen from a patient showing thickening of the muscularis mucosae and fibromuscular proliferation (hematoxylin-eosin, ×80).

A statistically significant difference was observed for edema of lamina propria ($P < .01$) and a decreased villous/crypt ratio ($P < .01$) in duodenal and jejunal biopsy specimens.

Thickened muscularis mucosae and fibromuscular proliferations in the lamina propria stained positively with van Gieson's stain, whereas thickened vascular walls stained with periodic acid–Schiff, but were negative with van Gieson's stain.

Morphometric Assessment

The mean diameter of capillaries and the thickness of capillary wall were statistically greater in patients with portal hypertension compared with control subjects (see Tables 2 and 3).

Correlation With Clinical and Endoscopic Findings

Jejunal changes were more frequently associated with histologic changes in the duodenum (87%), followed by the antrum (79%) and the fundus (68%), but the difference was statistically not significant. In three patients, only jejunal changes were observed. A significantly higher number of patients undergoing sclerotherapy had portal hypertensive vasculopathic changes in biopsy specimens from all four sites (fundus, antrum, duodenum, and jejunum) than did those who had not undergone sclerotherapy (55% *vs* 23%; $P < .001$; Table 4). No such correlation was observed in relation to the grades of esophageal varices and the severity of hepatic disease as judged by the Child-Pugh score.

Evidence of thickened capillary walls was observed in a significantly higher number of duodenal (17 of 20 [85%]) and jejunal (18 of 20 [90%]) biopsy specimens from patients who had undergone sclerotherapy in contrast with those who had not undergone sclerotherapy (22 of 38 [58%] and 24 of 38 [63%] of duodenal and jejunal biopsy specimens, respectively; $P < .01$). However, no such association between an increase in the diameter of the vessels and sclerotherapy could be observed.

DISCUSSION

Awareness of the association between portal hypertension and changes in intestinal circulation has increased during the past decade. The predominant histopathologic change observed has been vasculopathy affecting the submucosal and mucosal vessels.

In earlier reports,[1,4–9,12] these changes have been described as dilatation, congestion, and ectasia, which is confusing. In the current study, simultaneous use of these terms has been avoided, and the histologic changes were divided into two groups depending on the thickening of the vascular walls. We found thick-walled mucosal vessels more frequently in patients with portal hypertension than we found dilated and congested vessels. Such dilated and congested gastric mucosal blood vessels have been found to be a poor marker of portal hypertension in earlier studies.[5,7,8]

Capillary dilatation has been observed to be nonspecific and may occur because of portal hypertension or other transient and even artifactual factors. Mucosal changes that resemble congestion may be caused by the pinch-avulsion technique with most commonly used biopsy forceps.[2]

None of the previous histologic studies have measured the vessel wall thickness, although there are reports of morphometric assessment of the size of the vessels in gastric (mean cross-sectional area) and jejunal biopsy specimens (maximum diameter).[9,13] In the current study, the maximum diameter of the mucosal capillaries and the maximum thickness of the capillary walls were measured. Although both variables were significantly greater in patients with portal hypertension compared with the findings in the control subjects, the difference in vessel wall thickness was more marked. Viggiano et al[2] also observed thick-walled dilated vessels in duodenal biopsy specimens. In a previous study of histologic changes in the jejunal mucosa of patients with portal hypertension, although a significant difference was seen in the diameter of blood vessels between control subjects and patients, more importance was given to the number

TABLE 4. NUMBER (PERCENTAGE) OF SITES SHOWING VASCULAR CHANGES IN RELATION TO TREATMENT WITH ENDOSCOPIC SCLEROTHERAPY

No. of Sites Involved	*Treated (n = 20)*	*Not Treated (n = 38)*
4	11 (55)	9 (24)
3	5 (25)	8 (21)
2	2 (10)	9 (24)
1	2 (10)	5 (13)
0	0 (0)	7 (18)

of blood vessels per villus in jejunal mucosa, and the thickness of vessel walls was not considered important.[9]

A peculiar feature noted in the current study was the exclusive presence of dilated thick-walled vessels without red blood cells in the lumen in duodenal and jejunal biopsy specimens from patients with portal hypertension. None of the specimens from the control subjects showed this feature. This is probably due to the rigidity of the thickened vessel walls, which prevents the vessels from collapsing even when the portal pressure is reduced. Similar changes have been observed in chronic venous congestion of the spleen in which the red pulp is suffused with red blood cells during the early phase of portal hypertension. However, the pulp becomes more fibrous and cellular with time, and the sinusoids seem to be dilated because of rigidity of their walls.[14] This suggests that dilated and congested vessels in patients with portal hypertension are a transient and reversible phenomenon, but dilated vessels with irregular thickening represent chronic and more persistent changes.

The association of other abnormal histologic variables with thick-walled vessels, rather than that with congested vessels lacking thickened walls, indicates that a chronic increase in the luminal pressure may also lead to mucosal edema and loss of villous architecture. These findings are similar to a previous report on patients with portal hypertension, in which edema of the lamina propria and dilated and ectatic capillaries were seen in all the gastric biopsy specimens from patients with a "mosaic pattern" shown by upper gastrointestinal endoscopy.[15] Nagral et al[9] also have observed an increased prevalence of mucosal edema and thickened muscularis mucosae in jejunal biopsy specimens from patients with portal hypertension.

The thickened muscularis mucosae and increased fibrous tissue in the lamina propria that we observed showed an increased amount of collagen by van Gieson's stain. This was most probably due to the chronic ischemia of the mucosa in patients with portal hypertension.[16–18]

The presence of vascular changes in all four sites (ie, fundus, antrum, duodenum, and jejunum) in a significantly higher number of patients who had received sclerotherapy than those who had not undergone sclerotherapy suggests that obliteration of esophageal collateral vessels by endoscopic sclerotherapy may lead to extension of portal hypertensive vasculopathic changes to more distal organs, such as the duodenum and jejunum. Such lesions may contribute to occult blood loss and lead to anemia as observed in an earlier study.[19]

We found that portal hypertensive enteropathic changes are characterized by the presence of thick-walled dilated mucosal vessels with marked edema of the lamina propria, a decreased villus/crypt ratio, and fibromuscular proliferation in the lamina propria. These vascular and mucosal changes form a spectrum of changes that occur throughout the gastrointestinal tract in patients with portal hypertension. These changes may lead to occult blood loss and anemia.

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