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Gastric red spots in patients with cirrhosis: Subclinical condition of gastric mucosal hemorrhage?

Tadashi IWAO, Atsushi TOYONAGA, and Kyuichi TANIKAWA
Second Department of Medicine, Kurume University School of Medicine, Kurume 830, Japan

Summary: The present study was intended to assess the incidence and the nature of gastric red spots (GRS) in patients with liver cirrhosis. Endoscopically, GRS was more frequently observed in patients with cirrhosis (n=146) than those without cirrhosis (n=103) (43.2% vs. 4.8%; P<0.001). There was no relationship between the incidence of GRS and the severity of cirrhosis or the size of varices. Portal venous pressure was higher in cirrhotics with GRS (n=21) than those without GRS (n=25) (33.7±6.0 mmHg vs. 28.2±4.8 mmHg; P<0.001). Morphometric analysis using the biopsied specimens was made in 16 cirrhotics with GRS, 12 cirrhotics without GRS, and 15 non-cirrhotics. The capillary bed occupation ratio (vascular area/mucosal area) was higher in cirrhotics with GRS (9.3±4.0%) than those without GRS 84.1±1.1%) or the non-cirrhotics (3.4±9.8%) (P<0.005, P<0.005), while there was no significant differences in the number of capillaries per unit area. Infiltrating inflammatory cell count was similar among the three groups. Extravascular red blood cell count per unit area was higher in cirrhotics with GRS (29.7±31.4) than those without GRS (5.4±5.1) or non-cirrhotics (5.4±6.3) (P<0.05, P<0.01). Furthermore, extravasation of red blood cells through defective portion of the endothelium and interposition of red blood cells in interepithelial spaces were observed electron microscopically in cirrhotics with GRS. These results indicate that (a) the nature of GRS in cirrhotics is preexistential capillary ectasia with intramucosal hemorrhage which is caused by high portal pressure and (b) the GRS in cirrhotics might be a subclinical condition of gastric mucosal hemorrhage.
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Key words: *gastric red spots; liver cirrhosis; morphometric analysis; portal hypertension*

Introduction

Endoscopic investigations for upper digestive tract hemorrhage in patients with liver cirrhosis have clarified that, in addition to rupture of esophageal varices as the principal cause, bleeding from the stomach unexpectedly occupies in as high a proportion as 30-52%[1-11]. Furthermore, the principal cause of this gastric bleeding is hemorrhagic gastritis. Enquist[11], who examined numerous autopsy cases, reported that, in the gastric mucosa of patients with cirrhosis, intramucosal bleeding and erosion were observed with a 3- to 5-fold frequency compared with control autopsied cases. When viewed from the standpoint of gastric hemorrhage, it is recognized that cirrhotic patients frequently exhibit so-called hemorrhagic gastritis.

On the other hand, it is especially noteworthy that routine endoscopic examination of patients with cirrhosis has been well documented that gastric red spots in proximal part of the stomach (GRS hereinafter) are observed with a high frequency[12-15]. Conversely, such a state is rarely observed in non-cirrhotic patients[13,15].

Since it was suggested that there may be some

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Address for correspondence: Tadashi Iwao, M.D., The Second Department of Medicine, Kurume University School of Medicine, 67 Asahi-Machi, Kurume 830, Japan.
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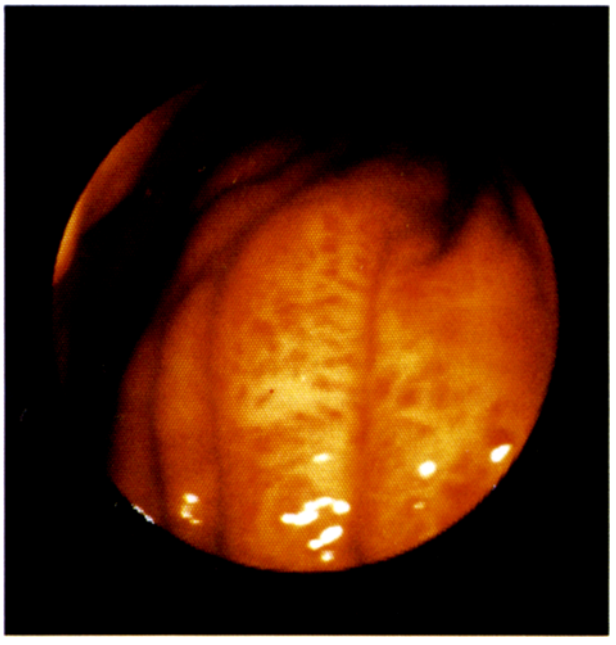

Fig. 1 The endoscopic findings show gastric red spots in a patient with cirrhosis. Note multiple flecked red spots in the upper corpus of the stomach along the greater curvature.

relationship between the presence of GRS and hemorrhagic gastritis, clinico-endoscopic, hemodynamic, and histopathologic investigations on the GRS were performed in the present study.

Materials and Methods

Clinical and endoscopic study

Using a flexible fiberscope (GIF-Q_{10} Olympus, Tokyo, Japan), endoscopic examination was performed on 146 patients with histologically or clinically proven liver cirrhosis (mean age 53.2 years, ranging from 31 to 76; 88 males and 58 females) and on 103 patients without liver cirrhosis (mean age 56.8 years, ranging from 29 to 89; 60 males and 43 females), and the frequency of GRS was investigated (**Fig. 1**).

In the patients with cirrhosis, on the basis of presence or absence of GRS, we further examined from the view of the severity of cirrhosis by Pugh-Child's classification[16] and the size of esophageal varices. The description of esophageal varices was conducted according to the Japanese criteria[17].

Measurement of portal venous pressure

After an overnight fast, patients were brought to the vascular catheter room and positioned supinely. Under local anesthesia, percutaneous transhepatic portal vein catheterization (5.5-F) was carried out as previously described[18] and portal venous pressure was directly measured.

Measurement of portal venous pressure was performed in 46 patients with cirrhosis (mean age 55.7yrs; 30 males and 16 females) who were divided into two groups; i.e., 21 patients with GRS and 25 patients without GRS. All patients gave their informed consent to participate in the study.

Histological observation of the gastric mucosa

Using a biopsy forceps under endoscopic observation, 4 to 6 specimens were collected from the greater curvature of the upper body of the stomach in 16 cirrhotic patients with GRS, 12 cirrhotic patients without GRS (as disease control), and 15 non-cirrhotic patients with normal gastric mucosa endoscopically and normal ranged biochemical data (as normal control). All patients gave their informed consent to participate in the study.

Light microscopic observation: The biopsied specimens obtained were fixed with 10% formalin, subjected to tangential orientation stereomicroscopically, sliced, and stained with hematoxylin eosin. The specimen preparations for each case were subsequently photographed under a 100-fold magnification focusing at the proximity of the epithelium. Five photographs were randomly sampled, and in each of them a standard line having a depth of 100 μm immediately below the epithelium was drawn, and thus a closed plane was prepared. This closed plane included a large group of capillaries (17 to 52 capillaries per case; mean 31.1 capillaries) and a few collecting venules. A morphometric analysis using a semiautomatic computerized imaging analyzer (Nikon) was performed to assess capillary vasculature as the following parameters (thus a few collecting venules were excluded in this analysis). The first parameter is the mean capillary diameter; deeming the cross-section of a capillary under observation as psuedocircular or pseudoelipsoidal in shape, defining the longest of the lines drawn per-

Table 1 Frequency of gastric red spots in cirrhotics and non-cirrhotics

	Cirrhotics	Non-cirrhotics	Total
GRS (+)	63 (43.2%)	5 (4.8%)	68
GRS (−)	83 (56.8%)	98 (95.2%)	181
Total	146	103	249

GRS, gastric red spots. $P<0.001$

Table 2 Frequency of gastric red spots and severity of cirrhosis

	GRS (−)	GRS (+)	Total
Pugh-Child's A	23 (43.5%)	29 (56.5%)	52
Pugh-Child's B	34 (61.4%)	21 (38.6%)	55
Pugh-Child's C	24 (61.5%)	15 (38.5%)	39
Total	81	65	146

GRS, gastric red spots. No significant difference

Table 3 Frequency of gastric red spots and size of esophageal varices

	GRS (−)	GRS (+)	Total
Small varices	56 (58.0%)	40 (42.0%)	96
Large varices	26 (52.2%)	24 (47.8%)	50
Total	82	64	146

GRS, gastric red spots. No significant difference
Small varices, F_1; Large varices, F_2 or F_3

pendicularly to the maximal diameter as the diameter of capillary, the mean diameter being calculated for each case. The second is the mean capillary area; defined as the cross-sectional area calculated as the mean value for each case. The third is the capillary bed occupation ratio; the proportion occupied by capillary bed in the lamina propria in the above defined plane in each case. Finally, the number of capillaries per unit area is defined that the number of capillaries seen per 10^5 μm^2 of lamina propria in the range defined earlier in each case. Additionally, the number of infiltrating inflammatory cells and extravascular red blood cells were counted in the range defined above.

Electron microscopic observation: The biopsy specimens obtained were fixed with formaldehyde and glutaraldehyde solution for 2 hours, tangentially orientated by stereomicroscopy, sliced, rinsed with sucrose solution, fixed with osmium tetroxide, dehydrated using a series of aqueous ethanol solutions, and plate-embedded in an epoxy resin. Slices of several-μm thickness were then prepared using a glass knife from the epon-embedded blocks. These were stained with 1% toluidine blue and the neighborhood of the epithelial lining was trimmed away. Super-thin slices were subsequently prepared from these epon-embedded blocks, and they were photographed under observation using a JEM-100S (JEOL) under a 1,000 to 6,000-fold magnification for the whole image and a 30,000-fold magnification of the fenestration of the capillary. Regarding the fenestration, a mean diameter was measured in each case (40 to 62 per case) to be subjected to comparative examination.

Statistical analysis

All results were expressed as mean±SD. Student's t-test for unpaired data and the χ^2 test were employed. Significance was established at $P<0.05$.

Results

Clinical and endoscopic analysis

The frequency of GRS was 4.8% for non-cirrhotic patients and 43.2% for cirrhotic patients, the latter being more closely associated with GRS ($P<0.001$) (**Table 1**). In the cirrhotic patients, relationship between the incidence of GRS and the severity of liver cirrhosis resulted in 56.5% concomitance in Grade A, 38.6% in Grade B, and 38.5% in Grade C, indicating no significant correlation (**Table 2**). Additionally, the relationship between the frequency of GRS and the size of varices (F_1: small varices, F_2 and F_3: large varices) indicated no significant difference (small varices vs. large varices; 47.8% vs. 42.0%) (**Table 3**).

Analysis between portal venous pressure and GRS

When portal venous pressure was studied in correlation to the presence or absence of GRS, the presence of GRS was associated with significantly higher portal venous pressure (33.7±6.0

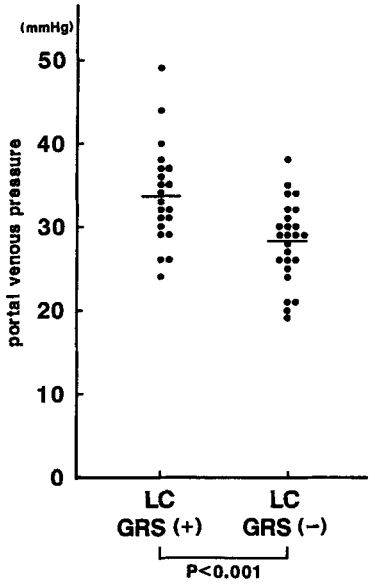

Fig. 2 Individual values of the directly measured portal venous pressure in cirrhotics with gastric red spots and those without gastric red spots. The difference between the two groups is highly significant (P<0.001). LCGRS (+), cirrhotics with gastric red spots; LCGRS (−), cirrhotics without gastric red spots.

mmHg vs. 28.2±4.8 mmHg; P<0.001) (**Fig. 2**).

Morphometric analysis

All results are summarized in **Table 4.**

Vascular system: More dilated capillary diameters were found in cirrhotic patients with GRS (13.5±1.8 μm) compared with patients in the control group (8.2±0.9μm) cirrhotic, patients without GRS (9.8±1.7 μm) (P<0.005, P<0.005). The capillary diameter of cirrhotic patients without GRS was significantly larger than that seen in the control group (P<0.005). Mean capillary area of cirrhotic patients with GRS (369.1±100.7 μm^2) was more extended than that of the control group (147.1±42.1 μm^2) or that of cirrhotic patients without GRS (190.5±50.4 μm^2) (P<0.005, P<0.005). Cirrhotic patients without GRS exhibited a more extend area than the control group (P<0.05). Cirrhotic patients with GRS exhibited a clearly higher in capillary bed occupation ratio (9.3±4.0%) than either that of the control group (3.4±0.8%) and that of cirrhotic patients without GRS (4.1±1.1%) (P<0.005, P<0.005). The capillary bed occupation ratio of cirrhotic patients without GRS was higher than the controls, but the difference was not significant. There was no significance among cirrhotic patients with GRS (25.3±9.0), those without GRS (23.1±9.9), and the controls (24.0±6.8) in the number of capillaries per unit area.

Inflammatory cellular infiltration: No significant difference in the number of infiltrating inflammatory cells was seen among cirrhotic patients with GRS (32.7±17.0), those without GRS (41.9±19.7), and the control group (41.8±6.4)

Extravascular red blood cells: Cirrhotic patients with GRS (29.7±31.4) showed a higher value than the control group (5.4±6.3) and cirrhotic patients without GRS (5.4±5.1) (P<0.01, P<0.05). Cirrhotic patients without GRS did not

Table 4 Morphometric analysis

	Controls (15)	Cirrhotics without GRS (12)	Cirrhotics with GRS (14)
Capillary diameter (μm)	8.2±0.9	9.8±1.7^{y}	13.5±1.8^{b,q}
Capillary area (μm^2)	147.1±42.1	190.5±50.4^{x}	369.1±100.7^{b,q}
Capillary bed ocuppation ratio (%)	3.4±0.8	4.1±1.1	9.3±4.0^{b,q}
Number of capillaries per unit area (n/10^5 μm^2)	24.0±6.8	23.1±9.9	25.3±9.0
Number of inflammatory cells per unit area (n/10^4 μm^2)	41.8±6.4	41.9±19.7	32.7±17.0
Number of extravascular RBC per unit area (n/10^4 μm^2)	5.4±6.3	5.4±5.1	29.7±31.4^{a,p}
Width of fenestration (nm)	53.4±1.9	53.3±2.2	52.0±3.5

All results are expressed as mean±SD. Numbers in parentheses indicate number of patients.
GRS, gastric red spots; RBC, red blood cells.
a; P<0.01, b; P<0.005 in unpaired t-test compared between controls and cirrhotics with gastric red spots.
p; P<0.05, q; P<0.005 in unpaired t-test compared between cirrhotics without gastric red spots and cirrhotics with gastric red spots.
x; P<0.05, y; P<0.005 in unpaired t-test compared between controls and cirrhotics without gastric red spots.

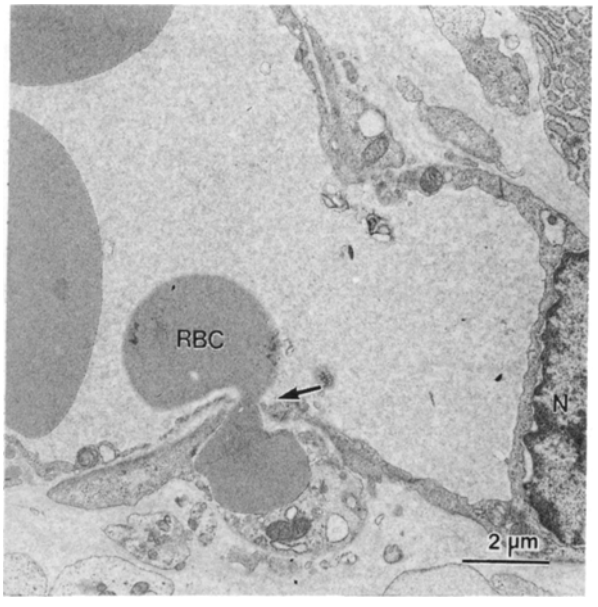

Fig. 3 The electron micrograph (×5,800, original magnification ×2,000) shows extravasation of a red blood cell through the defective portion of the endothelium (arrow) in a cirrhotic patient with gastric red spots. RBC, red blood cell; N, nucleus of the endothelial cell.

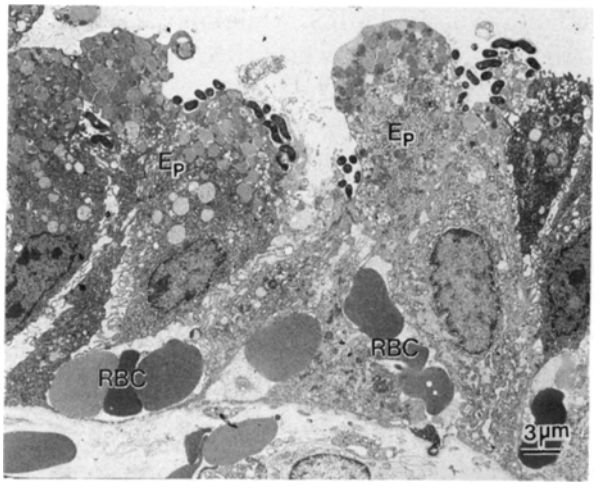

Fig. 4 The electron micrograph (×1,700, original magnification ×650) shows interposition of red blood cells in inter-epithelial spaces in a cirrhotic patient with gastric red spots. RBC, red blood cell; EP, epithelial cell.

show significant difference when compared with the control group.

Width of fenestration of capillary: There was no significant difference in the width of fenestration among cirrhotic patients with GRS (52.0±3.5 nm), those without GRS (53.3±2.2 nm), and the controls (53.4±1.9 nm).

Additional important information

In cirrhotic patients with GRS, extravasation of red blood cells through defective portions of capillary endothelium and interposition of red blood cells in inter-epithelial spaces were observed electron microscopically (**Figs. 3 and 4**). These findings were not detected in any other groups.

Discussion

Although it is needless to address the fact that the rupture of esophageal varices is the principal cause of upper digestive tract hemorrhage in patients with cirrhosis[1-11], gastric bleeding observed endoscopically in approximately half of upper digestive tract hemorrhages and hemorrhagic gastritis occupying of such majority cases[1-9] hold an important clinical significance. Moreover, hemorrhagic gastritis is accompanied by liver cirrhosis as the underlying disease in many cases[9,11]. Sarfeh and coworkers[20] compared the gastric mucosa of rats with portal hypertension with that of the control rats and pointed out that the former exhibited damaged gastric mucosal barrier and that the gastric mucosal disorder is enhanced after ethanol load. In addition, Lebrec and coworkers[21,22] reported that portocaval shunt and propranolol were clinically effective in treatment of hemorrhagic gastritis in patients with cirrhosis. These experimental and clinical information suggest that portal hypertension is closely related to hemorrhagic gastritis.

In addition to these, many other researchers reported the occurrence of GRS in the proximal portion of the stomach detected at routine endoscopic examination of patients with cirrhosis; they are described as: discrete red spots[12], small erythematous area outlined by subtle yellowish network[13], or non-confluent small red spots[23]. On the other hand, such GRS are reported to be seldom detected in non-cirrhotic patients[13,15]. In our present study also, 43.2% of the cirrhotic

patients exhibited GRS, while only 4.8% of non-cirrhotic patients showed GRS, supporting with the previous report. The incidence of GRS in relation to the severity of liver cirrhosis, failed to prove a correlation. However, when investigated with respect to portal venous pressure, cirrhotics with GRS showed significantly higher values than those without GRS (19.5% in relative difference and 5.5 mmHg in absolute difference). Thus, the possible mechanism of GRS occurrence may include portal hypertension rather than the progression of liver cirrhosis. In addition, no correlation was found between GRS appearance and the size of esophageal varices. This can be interpreted first to mean that the size of varices is not related to portal venous presure[7], and secondly because congestive hemodynamic state is relaxed since the development of the varicose vein acts, at least in part, decompression on portal pressure as a drainage vein (unpublished observation in our laboratory).

Histlogically, according to McCormack and coworkers[12], small numbers of infiltrating inflammatory cells are detected in GRS while what are present are the congestive dilatated vessels, the state of which should be termed "congestive gastropathy". Hashizume and coworkers[24] also reported in their study, using silicon rubber vascular casts, that the gastric mucosa of cirrhotic patients exhibited dilatated capillary vessels. Quintero and colleagues[23] light microscopically analyzed the red spots in the antrum of the stomach and concluded that this was due to vascular ectasia. In the present study, morphometric analysis with various parameters, focusing on the construction of GRS in a more objective manner, was established. Analysis revealed that the group of cirrhotic patients with GRS exhibited higher values of mean capillary diameter and area, and that they showed a higher capillary bed occupation ratio in the gastric mucosa, than in those without GRS or the controls. Although some previous reports[10,13] described that, in addition to increased vessel diameter, the number of vessels are increased, the present analysis clarified, however, that there is no difference in the number of vessels per unit area among these three groups. Moreover, the number of infiltrating inflammatory cells per unit area did not differ among the three groups observed. Judging from the above results, it was concluded that the nature of GRS is, unlike neovascularization, ectasia of pre-existent capillaries. To further investigate the involvement of intramucosal hemorrhage, the number of extravascular red blood cells was counted. This examination clarified that, in the cirrhotic group with GRS, higher values were observed, with statistical significance, compared with the cirrhotic group without GRS or the control group. Although it cannot be denied that traumatic hemorrhage can occur at biopsy, the presence of GRS is related not only to vasodilatation but also to intramucosal hemorrhage.

Regarding the mechanism of vasodilatation in cirrhotics with GRS, portal hypertension was firstly considered. In fact, as stated earlier, cirrhotics with GRS showed a more elevated level of portal venous pressure than those without GRS. Furthermore, several reports[14,15,25-27] indicated that since the gastric mucosa in patients with cirrhosis demonstrated a hemodynamically increased gastric mucosal blood volume and reduced oxygen saturation, a congestive hemodynamic status is thought to be present in the gastric mucosa in patients with cirrhosis. It seems that our present morphologic results are related to such hemodynamic alterations. On the other hand, it has been widely known that cirrhotic patients tend to hyposecrete gastric acid[28-30]. Thus, through a negative feedback mechanism, hypergastrinemia is manifestated and gastrin subsequently acts to dilate the vessels[23]. Since various degrees of malmetabolism are expected in liver cirrhosis, further investigations are required from this view point.

There are a few reports of ultrastructual alteration of gastric mucosal vasculature in portal hypertensive gastric mucosa. Sarfeh and coworkers[31] reported expansion of endothelial cytoplasm, numerous microprojections into the microvascular lumina, numerous pinocytic vesicles, thickness of basal membrane, and reduction of capillary luminal area in experimental portal hypertensive rat model. Unlike this report,

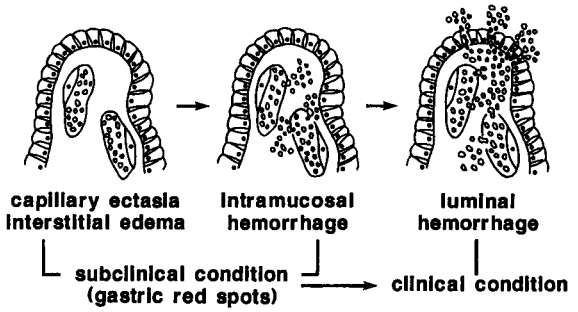

Fig. 5 One of the assumed processes of gastric hemorrhage in portal hypertensive gastric mucosa.

Kato[32] described that there were some abnormalities, such as enlargement of capillary diameter, thinning of endothelium, and thinning of basal membrane, in patients with portal hypertension and cirrhosis. In addition, Kato[32] reported a significant opening of endothelial fenestrations. Conversely in the present study, unlike Kato's report, the width of fenestrations in the group of cirrhotics with GRS did not show any significant difference from not only that of the group of cirrhotics without GRS but also that of the control group. The reason for the discrepancy between the previous report and the present report is not clear. However, it is considered that the elevation of intravascular pressure did not always lead to the opening of the fenestrations, since electrolytes and other smaller sized molecules can freely pass through these pores[33]. However, when chronic elevation of intravascular pressure is sustained, endothelial cells will become increasingly more fragile through the influence of the accompanying hypoxial state, leading to damage to endothelial cells and to the capillary rupture shown in **Figure 3**. Furthermore, it is noteworthy that there was interposition of red blood cells in interepithelial spaces as shown in **Figure 4** in cirrhotic patients with GRS. These findings suggest the hypothesis of a mechanism of gastric hemorrhage in patients with portal hypertensive gastric mucosa as shown in **Figure 5**, i.e., the process may be that, first, damage to endothelial cells in dilated capillaries is caused, this assumes the form of intramucosal hemorrhage (these changes are observed as GRS endoscopically), subsequently leakage occur among epithelial cells, and finally bleeding into the lumen takes place. In fact, we have frequently encountered, during emergency endoscopy, oozing-like bleeding from extended gastric mucosa or gastric hemorrhae without erosive lesions in patients with cirrhosis[9]. This clinical information would also support this bleeding mechanism. Moreover, since there is an abnormal fibrinolytic system, according to Minami in our laboratory (personal communication), in addition to congestive hemodynamics, exosorptive hemorrhage on the basis of the above mentioned could be assumed, even if apparent erosion is not clear. However, since there is a controversy concerning microvascular alterations in portal hypertensive gastric mucosa, further examination on this matter, including the solution of the precise mechanism of gastric mucosal hemorrhage, should be undertaken in the future.

In conclusion, the occurrence of GRS in patients with cirrhosis was related to high portal hypertension and the nature of GRS in patients with cirrhosis was not inflammatory alteration, but ectasia of preexistent capillaries with intramucosal hemorrhage. Thus, the GRS correspond to the category of portal hypertensive gastropathy[34], and might be a subclinical condition of gastric mucosal hemorrhae (so-called hemorrhagic gastritis) associated with cirrhosis.

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