Chapter 2
Pathological Findings for Esophageal Varices

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Abstract The citing of pathological findings regarding the esophageal varices is uncommon.
Accordingly, the authors report on the histology of esophageal varices including studying failure images of esophageal varices by pathologists and a specialist in endoscopy removing the lower esophagus and stomach at an autopsy en bloc and injecting a liquid into which we mixed gelatin and barium into varicose blood vessels. Also, we compared this histology with endoscopic findings and examined the angioarchitecture of the lower esophagus and discussed the origin of the esophageal variceal rupture.

Keywords Pathology · Esophageal varices · Esophageal variceal rupture

2.1 Introduction

Esophagogastric varices are the most important pathology associated with portal hypertension. Portal hypertension is a pathological condition of hypertension that develops due to abnormalities in the blood circulation through the portal system. This hypertension then leads to the development of secondary symptoms such as esophageal and gastric varices, splenomegaly, and ascites. The term "portal hypertension" thus does not refer to a single disease entity. The background involves various pathologies, and the underlying causes of the hypertension also vary. However, the cause of many of the diseases involved is emphatically determined to be

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hypertension due to increased blood flow resistance at sites in the portal system or the hepatic venous system. In the healthy human body, the blood flow in the portal veins is from the lower esophageal and upper gastric region through the left gastric vein and portal veins to the liver. However, if the blood flow through the portal vein is impaired, portal pressure rises and portal vein blood flow increases. The blood flow in the vicinity then reverses in direction, and a hepatofugal collateral circulation develops from the portal vein to the upper gastric and lower esophageal regions. A large volume of blood then flows through the blood vessels in the walls (lamina propria, submucosa) of the upper gastric and lower esophageal regions. The blood vessels dilate and meander, forming protrusions on the surface of the esophagus and resulting in the development of esophageal varices. Here, we report the results of a study conducted jointly by clinicians and pathologists on described pathomorphological findings such as the red color sign observed on endoscopy, with a focus on the histology of the protrusions and rupture sites of varices, which have passed largely unreported.

Prior to the present research, we investigated the relationship between intraportal tumor thrombi and esophageal varices in patients with hepatocellular carcinoma [1, 2] and considered the question of how esophageal varices can best be understood as pathomorphological findings. The presence of tumor thrombi in esophageal varices at that time provided a hint, and in 1980 we began to study varices in earnest using the inspection procedures described below. At that time, endoscopic sclerotherapy was just beginning in Japan, and we were able to study untreated cases and also perform autopsies on cases in the early posttreatment stage. We were fortunate enough to be able to study 50 patients with untreated esophageal varices using a technique in which we injected a contrast agent (described below). Relatively few pathologists appear to have studied esophageal varices up to now, and it is easy to place a dogmatic interpretation on the various pathological findings. However, pathological findings such as bleeding from ruptured esophageal varices match clinical findings on emergency endoscopy, particularly the detailed findings from emergency endoscopy reported by Makuuchi et al. [3], which we consider provides some degree of objectivity.

2.2 Procedure for Inspection of Varices

Briefly, the stomach and esophagus are removed en bloc (up to the mid-esophagus) at the time of autopsy. Barium that has been added to gelatin is warmed to a liquid state and infused into the left gastric vein (gastric coronary vein) which supplies the varix. The specimen is chilled immediately after infusion and fixed in 10% formalin. An image is obtained using a Softex X-ray system, and the specimen is dehydrated in an ascending alcohol series and cleared with methyl salicylate solution. Macroscopic photographs are taken for examination. This method enables the specimen to be examined in a state more closely resembling the status during life [4–6]. Figure 2.1 shows a macroscopic image, soft radiograph, and transparent preparation

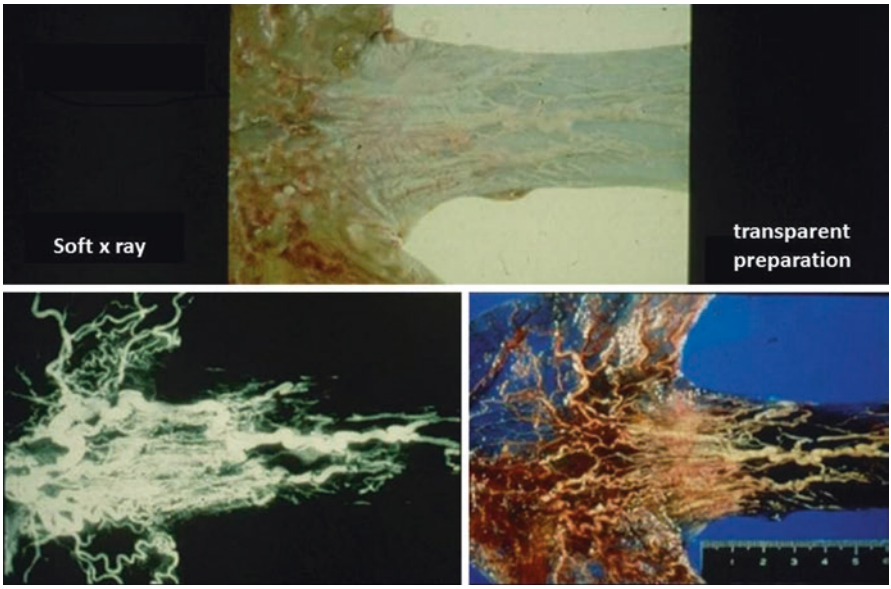

Fig. 2.1 Upper panel: Gelatin-barium injection preparation. Lower left: soft radiograph. Lower right: transparent preparation

for an esophagus and stomach that had been removed from a patient with esophageal varices and infused with the contrast agent. Problems associated with this type of examination involve the infusion pressure. However, our method is considered to apply almost no pressure to the varix, because the resected margins of the esophagus are opened, and the infusion of fluid does not increase the pressure.

In greater detail, our procedure is as follows. First, phosphate-buffered saline is injected into the left gastric vein, and the blood in the vessel is washed out. Next, 20% gelatin-barium (warmed to a liquid state) is infused. This infusion is stopped as soon as barium flows out of the cross section of the resected esophagus, and the organ is chilled in ice and fixed in ordinary formalin. After 1–2 days, macroscopic photographs are taken, and the specimen is sequentially dehydrated in an ascending alcohol series of 70, 80, 90, and 100%. The specimen is kept immersed in the absolute ethanol for 5–7 days, and after sufficient dehydration has been achieved, a transparent preparation is prepared using methyl salicylate. Only the blood vessels are visible in the transparent preparation, and the specimen is photographed after thorough macroscopic inspection prior to tissue specimen preparation. The key advantage of this procedure is to allow macroscopic observation, and tissue specimens can be prepared from sites identified as appropriate. This method of preparing tissue specimens allows accurate determination of the site of bleeding and subsequent detailed findings corresponding to endoscopic findings. For the excision of the histopathological specimens, the transparent preparations are returned to the original formalin-fixed specimens, and for the excision of microscopic specimens of

the esophagus, the specimens are cut into round slices so that all blood vessels at cross sections of the walls can be visually examined.

2.3 Vascular Architecture of the Normal Human Esophagus

Kegariesin [7] and Butler [8] investigated the vascular architecture of the normal human esophagus by injecting substances such as dyes into blood vessels and tracking their routes. However, it was not until 1966 that DeCarvalho [9] published a readily understandable detailed schematic of the routes of these blood vessels. That article surpassed its predecessors in terms of both detail and accuracy. However, we noted an error in the resulting schematic, in that Zone 3 (by DeCarvalho) showed a direct connection between the veins of the lamina propria and the netlike venous plexus immediately underlying the epithelium. However, our own studies of the relationship between those vessels have shown that the netlike venous plexus covers the entire esophagus and connects with the veins of the lamina propria at various sites. In the palisade zone (described below), fine blood vessels (reported as *sudare*-like veins) run almost in parallel over the entire circumference in the lamina propria, whereas only two to three fine blood vessels run in the submucosa. Our results in this regard are consistent with the findings of DeCarvalho.

2.4 Vascular Architecture in Esophageal Varices

Figure 2.2 presents our schema for the vascular architecture of the esophageal varices. This shows the palisade and truncal zones, in which three to four dilated, meandering vessels run, and their transitional area, termed the "critical area." The palisade zone cannot be accurately measured, but its length is within the range of 1.5–4.0 cm and is 2–3 cm in many patients. Figure 2.3 shows a macroscopic transparent preparation from a representative patient and the associated cross-sectional histological images. Vianna et al. [10] reported in 1987 regarding this classification and described a similar vascular architecture to that explored in our report. They described the area in which *sudare*-like veins ran as the palisade zone, and we therefore adopted the same expression. This zone represents the point of contact between the portal system and the systemic circulatory system. The lower boundary starts from the transitional area of the esophagogastric mucosa, while the upper boundary extends to the *hiatus* of the diaphragm and broadly corresponds to the abdominal esophagus. In a normal human body, blood in this area flows into the portal vein on the side of the gastric cardia, and in the neck the blood ascends from the esophageal veins through the azygos or semi-azygos vein to the superior vena cava.

Diseases that cause portal hypertension exhibit vascular resistance inside and/or outside the liver, and stasis of blood flow occurs in vessels such as the splenic vein and superior and inferior mesenteric veins, which are part of the portal system.

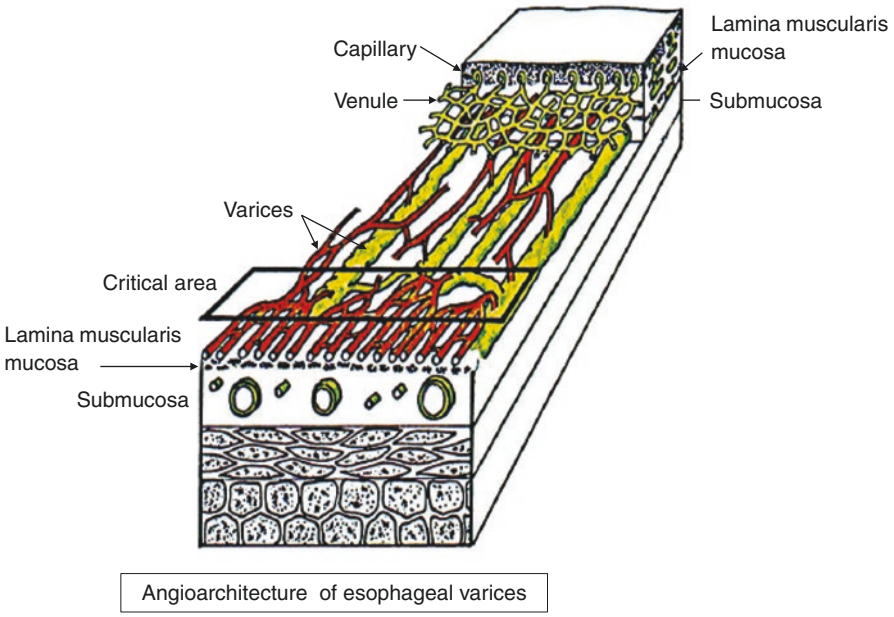

Fig. 2.2 Our schema of Zones 2–4 in the lower esophagus in portal hypertension with varices formation

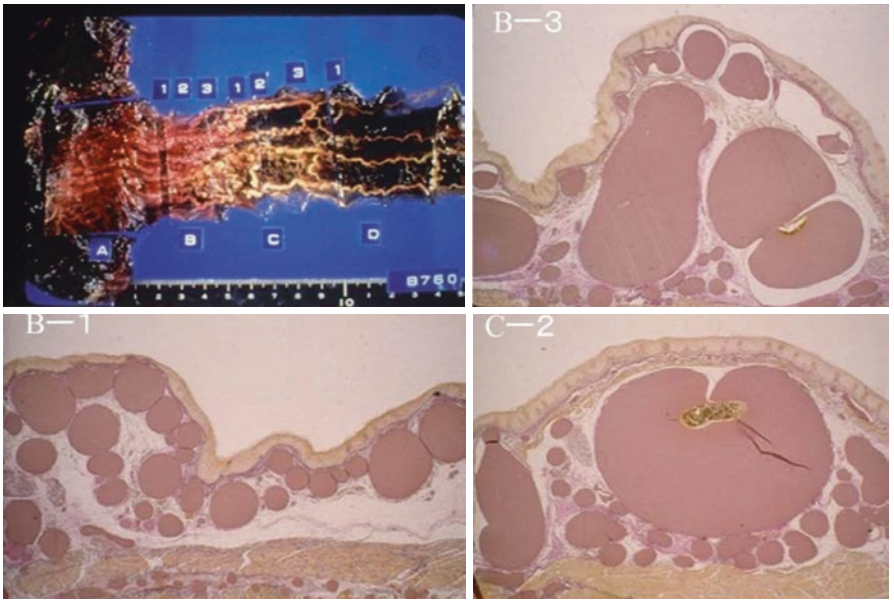

Fig. 2.3 The original transparent preparation (upper left) showing the various zones from which the corresponding sections were taken. B1, palisade zone; B3, transitional zone; C2, truncal zone ×20

If the stasis is severe, blood flow seeks escape in another direction. This is the hepatofugal collateral circulation, in which paths are opened to blood vessels such as the gastric and esophageal veins, the hemorrhoidal vein, and the abdominal wall veins.

Development of a hepatofugal collateral circulation leads to changes in the normal esophageal vascular architecture. That is, blood that was previously flowing from the palisade zone to the gastric cardia and then to the gastric coronary vein (left gastric vein) flows in a retrograde manner from the gastric coronary vein to the palisade zone. In this situation, the main blood circulation in the palisade zone flows in the lamina propria, and in the initial stage, the blood flows from the submucosa of the gastric cardia to the lamina propria of the palisade zone. The flow is then toward the blood vessels in the submucosa of the esophageal varices, but dilation of the blood vessels in the lamina propria gradually becomes more pronounced. As vascular resistance increases, the blood flow connecting the submucosa of the cardia to the submucosa of the esophageal varices (truncal) becomes the main flow. Schematically, these events lead to the blood flow changes shown in Fig. 2.4. Histological examinations of the palisade zone reveal the dilated blood vessels around the entire circumference of the lamina propria, but at the same time dilated blood vessels are also seen in the submucosa. Close inspection of these vessels run-

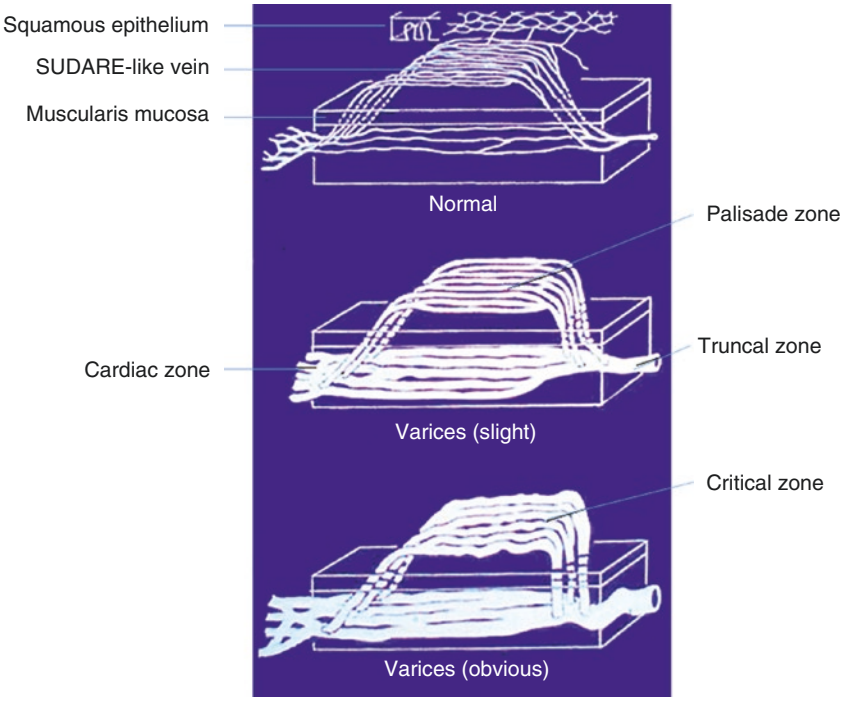

Fig. 2.4 Schema of dilated esophageal veins. The normal vein image has been slightly modified from the image of Dr. De Carvalho (1966)

ning in the submucosa reveals that, in addition to the inherently present vessels, other blood vessels come to run in the submucosa and are surrounded by the broken muscularis mucosae. On the basis of this finding, we surmised that those vessels do not represent new vessels per se but rather blood vessels that have been pushed into the submucosa from the lamina propria [11].

In summary, the vascular architecture of the esophagus in the palisade zone and other zones in patients with portal hypertension is characterized by large blood vessels (veins) in the submucosa, and although similarities exist between them, the basic vascular architecture differs. Such changes in the routes of blood vessels have never been reported, and this may be because only dilated vessels stand out in antemortem endoscopic findings.

Next, the critical area warrants attention. As was noted above, this area is the region in which ascending, dilated, meandering submucosal veins transition from the palisade zone to the truncal zone (Fig. 2.4). Clinically, the area in the lower esophagus that contains many ruptured vessels has been referred to as the critical area, and we have adopted this name since the transitional area contains many ruptured varices. In this area, many blood vessels, including the blood vessels seen in the lamina propria throughout its entire circumference and the previously mentioned blood vessels running in the submucosa, all flow into three to four blood vessels in the submucosa. This results in striking vascular piles. In addition, if we examine at cross sections of this region histologically, since vascular piles are apparent in patients with advanced varices, pronounced protrusions into the esophageal lumen are evident, and thinning of the epithelium of the esophagus is often seen (Fig. 2.3).

Since the vascular piles in the lamina propria flow into the blood vessels of the submucosa, sharp curves of the vessels are formed, resulting in elevated hemodynamic load. For these reasons, the blood vessels in this area are more likely to rupture. Of course, if erosion and/or inflammation are present in the esophageal mucosa, rupture in some sections of the esophageal varices may occur. However, in consideration of the vascular architecture, the palisade zone, which is rich in blood vessels in the lamina propria, may also have a high risk of rupture. Three to four variceal veins can be observed under modalities such as endoscopy as veins in the submucosa from the transitional area toward the oral side, narrowing with increasing proximity to the oral side.

These blood vessels in the submucosa anastomose with the other veins and sometimes pass through the muscle layer and anastomose with the paraesophageal veins. At the oral side from the transition area, the blood vessels of the lamina propria are markedly fewer in number compared with those of submucosa, and the possibility of rupture is considered small.

A cross section of the esophageal wall shows the presence of veins in the lamina propria over the submucosal veins (lumen side), and the netlike venous plexus immediately underlying the epithelium is seen over the lamina propria (representing a point of difference from the schema of DeCarvalho). Fine blood vessels running vertically from the venous plexus can be seen in the epithelium, and fine blood vessels can also be seen in the epithelium. As the varices develop further, the piles

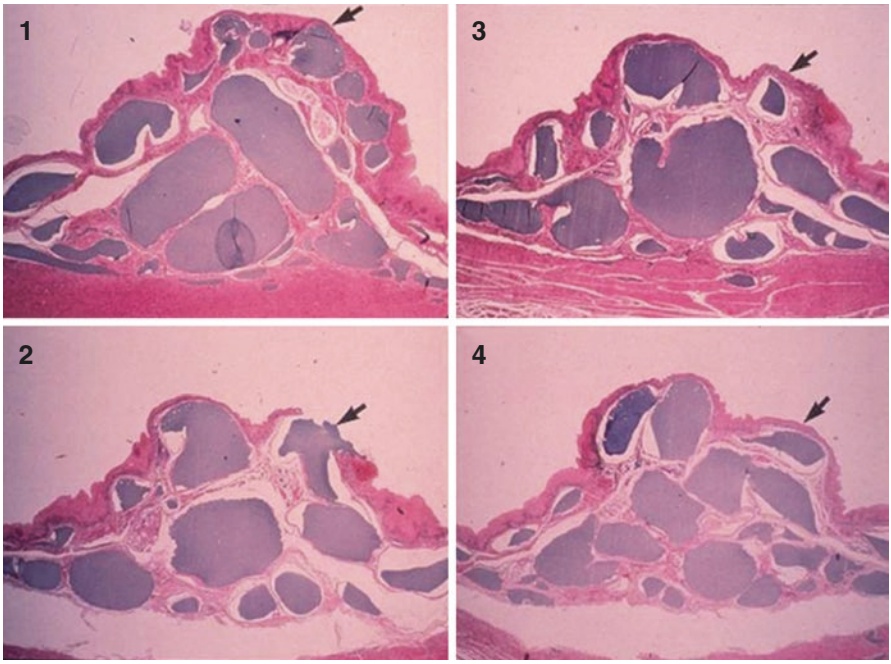

Fig. 2.5 Histological findings in serial sections made around the bleeding point. Section 2 is the bleeding point, and Sections 1, 3, and 4 are from areas near Section 2

of these blood vessels increase, the epithelium becomes thinner, and there the color sign becomes visible on endoscopy. Severe piles of varices are seen most frequently in the critical area. In fact, the bleeding point was identified in this area in all eight untreated patients we examined [4, 5]. If we inspect serial sections around the bleeding point, we find this corresponds to the red color sign (Fig. 2.5).

2.5 Bleeding Point of Esophageal Varices

The lower esophagus has been reported as being the most common site of bleeding of esophageal varices [12, 13], and while this has been readily confirmed clinically, there has been little confirmation from pathological studies of the site. Emergency endoscopy can now be performed safely, and findings such as the modes and sites of bleeding and the presence of post-bleeding fibrin clotting can now be elucidated [3]. However, anatomicopathological confirmation of the bleeding point at autopsy remains difficult, and this will become even more difficult in the future as most patients now undergo treatment before death.

Our group works in collaboration with clinicians, enabling the study of autopsy cases with ruptured esophageal varices by performing both more careful observa-

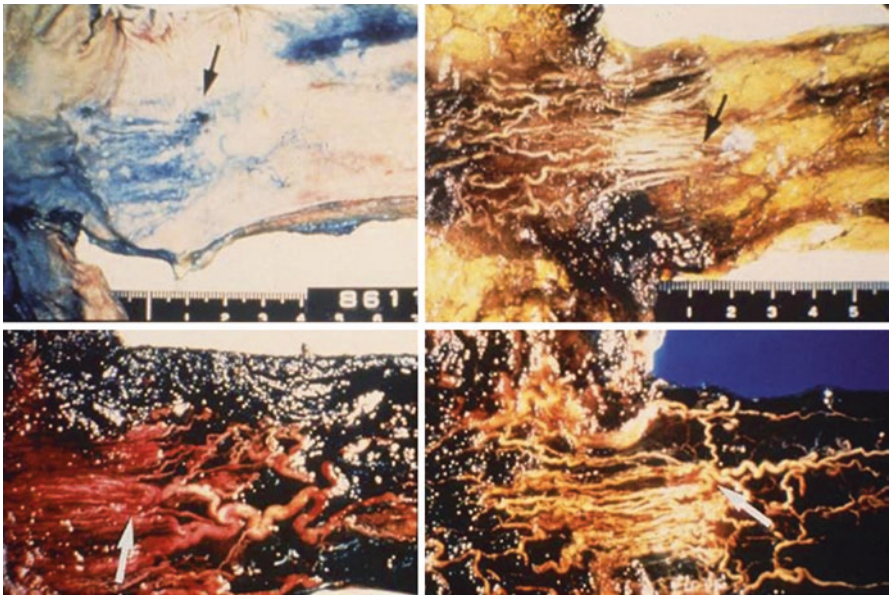

Fig. 2.6 The point of bleeding (arrows) from esophageal varices in four cases

tion of the esophagus and of inspection of sites of contrast agent leakage following infusion. Even in cases with no findings of contrast agent leakage, we prepare a serial tissue section of sites that macroscopically appear to be potential sites of rupture and inspect them microscopically. Our results have shown that the site of rupture bleeding is almost always in the region designated as the critical area (Fig. 2.6). Moreover, even in cases showing no leakage, the rupture hole can be histologically confirmed and is occluded by a blood clot [14]. This has also been elucidated from endoscopic observation of rupture sites. Our study of serial sections taken from around the rupture hole revealed a thinned squamous epithelium caused by blood vessels in the lamina propria. In addition, whether rupture bleeding is caused by elevated venous pressure or by inflammation has long been in question. Our pathological studies of the histogenesis of rupture cases have suggested that elevated venous pressure is a more likely cause of such ruptures.

2.6 Comparison with Endoscopic Findings

In 1980, the *General Rules for Recording Endoscopic Findings on Esophageal Varices* [15] was published in Japan, and reports stating that the red color sign (one of the endoscopic findings) is very closely related to bleeding gained attention. As a result, attention was focused on the pathology represented by the red color sign; however despite much discussion regarding histological findings, no conclusions

were able to be reached. The reason was that the collected tissues were unable to capture the varices as aneurysms. Later, the 1991 update of these General Rules [16] added emergency endoscopic findings, including findings of rupture bleeding.

To elucidate the relationship between the red color sign and the histological change, we then cut a large number of sections, mainly from the critical area, of ten patients with untreated esophageal varices who had been infused with gelatin-containing barium and who showed antemortem endoscopic findings of a rupture hole. This pathology was described, and endoscopic and histological findings were compared. On the basis of those results (Fig. 2.5), we were able to prove that the red color sign on endoscopic observations was consistent with findings of a thinned epithelium due to vascular piles in the lamina propria. In addition, images around the rupture hole in serial sections showed that the ultimately thinning epithelium partially corresponded to the rupture hole.

2.7 Summary

We applied a technique using a contrast agent in patients with untreated esophageal varices and reported pathomorphological images of variceal rupture mainly at the anatomical site of rupture bleeding that had not previously been elucidated. In addition, we compared endoscopic findings with histological findings and clearly showed histological images corresponding to the red color sign. We also discussed the mechanisms of variceal rupture.

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