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—Original Article—

EXTENT OF THROMBI FOLLOWING SCLEROTHERAPY OF ESOPHAGEAL VARICES

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Summary

Fifteen autopsy cases who died within 20 days after intravariceal endoscopic injection sclerotherapy using 5% ethanolamine oleate were examined to clarify the planar extent of thrombi. In 11 of the 15 cases, thrombi extended to part of the fundus of the stomach, as well as the lower esophagus. In addition to these cases, six autopsy cases who survived more than a month after the first injection were studied for the extent of thrombi on the basis of the angioarchitectural characteristics of esophageal varices. The extent could be divided into 3 groups: Group 1 included 5 cases with thrombosis in the main trunk of the varix alone, which connected with longitudinal veins (so-called "Venetian blind-like or sudare-like veins") running for 3–4 cm upward from the esophago-gastric junction. Group 2 included 9 cases with thrombosis in the main trunk and Venetian blind-like veins in the submucosa alone. Group 3 included 7 cases with thrombosis in the main trunk and Venetian blind-like veins in both the submucosa and lamina propria. These results obtained may provide basic information concerning this treatment. Furthermore, the mechanism of the recurrence of varices after eradication induced by treatment was discussed on the basis of the results.

Key Words: *Esophageal varices, Ethanolamine oleate, Injection sclerotherapy, Recurrence.*

Introduction

Esophageal morphological changes were analyzed in relation to the time intervals following endoscopic injection sclerotherapy (EIS) using 5% ethanolamine oleate in 26 autopsy cases[1]. This series showed that red thrombi obliterating varices were recognized within 20 days of treatment, and after a month, organization and shrinkage had occurred. Acute inflammation with tissue necrosis of the esophageal wall was present within 20 days, and after two and a half months, an almost cell-free fibrotic-sclerotic stroma was recognized. Thus, it is obvious that one of the purposes of EIS is to produce thrombi in varices. Nevertheless, to the authors' knowledge, there are few reports on the extent of thrombi after EIS[2].

Reappearance of varices or recurrent bleeding after treatment has been reported occasionally[3,4]: Ikeda et al.[5] reported that the incidence of "recurrence" of varices after EIS was

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statistically higher than that after esophageal transection surgery. In an examination of 34 cases for the recurrence of varices by the use of portography before and after EIS, recurrence was found to be statistically reduced in cases showing changes in the hemodynamics of the portal venous system, i.e., enlargement in the size of collaterals and/or the appearance of new ones[6]. However, details on the mechanism of the recurrence after EIS from a pathological standpoint have remained unknown. In the present study, the mechanism was discussed on the basis of the extent of thrombi in the esophagus and stomach.

Materials and Methods

This study consists of 15 with thrombi in varices out of 19 cases who died within 20 days after EIS using 5% ethanolamine oleate (short-term survival cases) and 6 who survived more than a month after the first injection (long-term survival cases). Case no. 22 was excluded because this patient underwent surgery for esophageal cancer. The case numbers correspond those in an earlier report[1].

In each case, 5 sections were obtained rou-

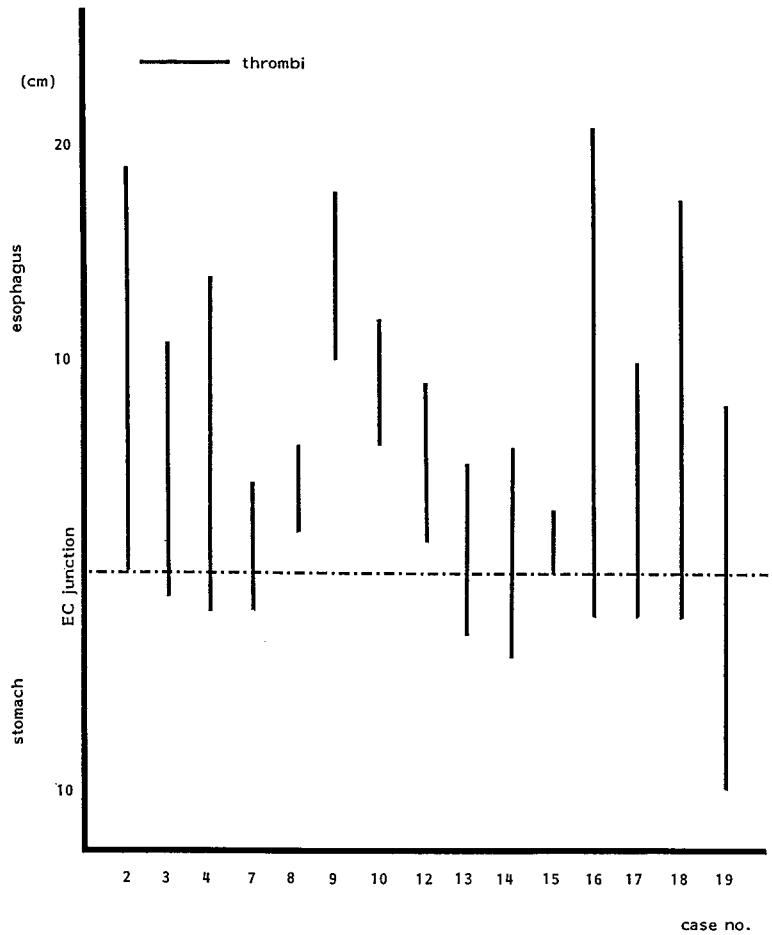

Fig. 1. The planar extent of thrombi in the short-term survival cases. Bars show the length of red thrombi. E-C junction: Esophago-cardiac junction

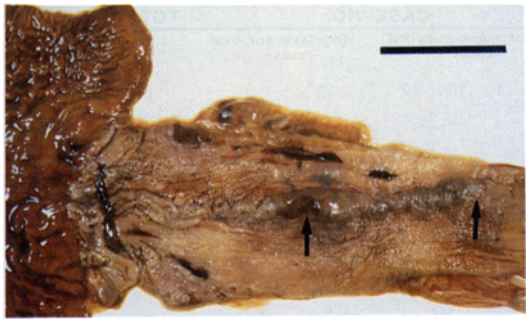

Fig. 2. Case no. 9. Arrows show red thrombi in a varix which appears as a blue line. Bar indicates 5 cm.

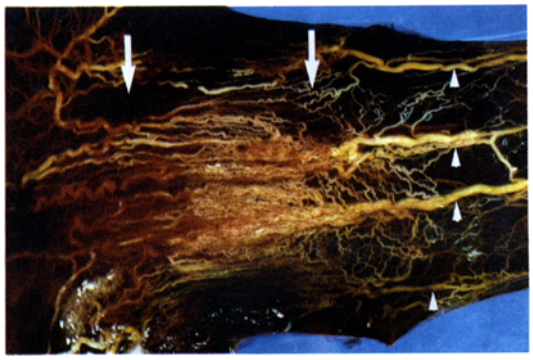

Fig. 3a. Transparent preparation of esophageal varices in the lower esophagus. The area shown by the two arrows shows so-called "Venetian blind-like veins". Arrow heads indicate four main trunks, which are observed as four varices endoscopically.

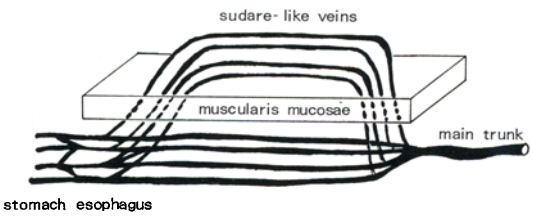

Fig. 3b. Schema of Venetian blind-like veins, from the picture of Dr. Noda[7]. Venetain blind-like veins originate at the esophago-gastric junction and run for approximatelly 3-4 cm upward, comprising of both subepithelial and submucosal veins. The main trunk in submucosa is formed to connect with Venetian blind-like veins.

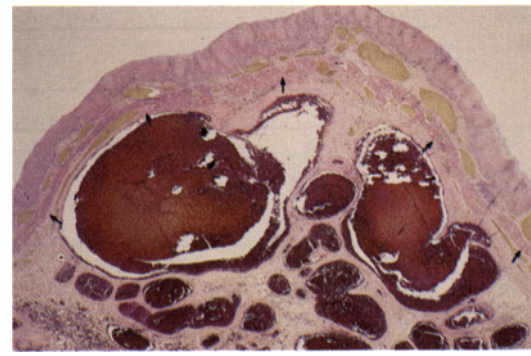

Fig. 5. Case no. 12. Specimen in the area of Venetian blind-like veins. The submucosal veins are occluded by red thrombi, but subepithelial veins are not thrombosed and are filled with a radiopaque mass. Arrows show the muscularis mucosae. (HE, ×20)

tinely every 2 cm from the esophago-gastric junction and stained with hematoxylin and eosin (H&E), elastica Van Gieson (EVG) and Azan-Mallory (Azan).

Gelatin solution containing contrast medium (7.5% gelatin with 50% barium) was injected into the esophageal vein through the left gastric vein in 5 cases at autopsy.

Results

I) Planar extent of thrombi: By careful gross and microscopical observation, the extent in the short-term survival cases could be demonstrated as shown in **Fig. 1** because red thrombi in the varix appeared as a blue line as shown in **Fig. 2**. In cases with thrombi in several varices, the longest thrombi were shown. In 11 of the 15 cases, red thrombi extended to part of the fundus of the stomach, as well as the lower esophagus, the remainder having thrombi more towards the oral side of the esophagus. However, in long-term survival cases, the extent could not be investigated because organized thrombi were not observed with the naked eye.

II) The extent of thrombi on the basis of the angioarchitectural characteristics of varices

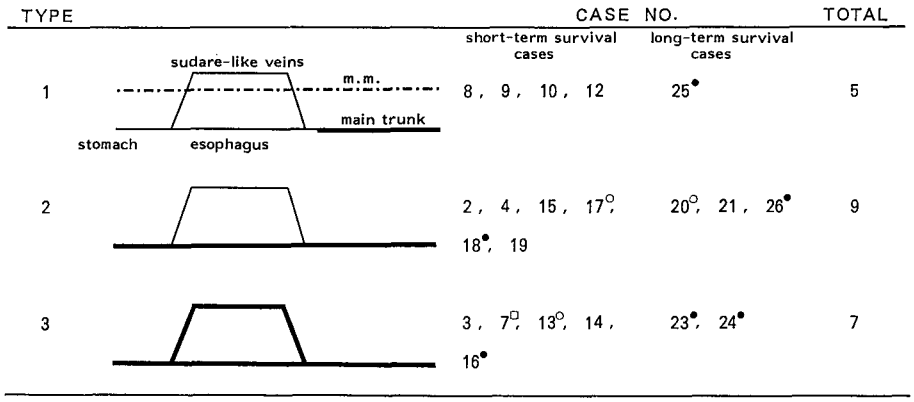

Fig. 4. The extent of thrombi on the basis of angioarchitectural characteristics of varix. Thick lines indicate thrombi in varices. No mark indicates the cases with thrombosis in one varices, circles those in two, open squares those in three, and solid dots those in four. m.m.: muscularis mucosae

(**Figs. 3a** and **3b**): The patients could be divided into 3 groups (**Fig. 4**): Group 1 included 5 cases of thrombosis in the main trunk of the varix alone. Group 2 included 9 cases of thrombosis in the main trunk and so-called "Venetian blind-like veins" in the submucosa. **Fig. 5** shows a case included in this group. Group 3 included 7 cases of thrombosis in the main trunk and Venetian blind-like veins in both the submucosa and lamina propria. Five out of 15 short-term survival cases and 5 out of 6 long-term survival ones had thrombi in 2-4 varices included in the same group, respectively.

Case Reports

The following are brief accounts of 3 patients chosen from the long-term survival ones.

Case 24. A 53-year-old man with liver cirrhosis and esophageal varices since 1980 came to the hospital for EIS of esophageal varices in January 1985 because he had twice suffered hematemesis two and six months earlier. Six injections were given over the course of 3 months, resulting in complete eradication of varices endoscopically. However, the patient died from repeated bleeding caused by hemorrhagic gastritis in August 1985. Pathological examination

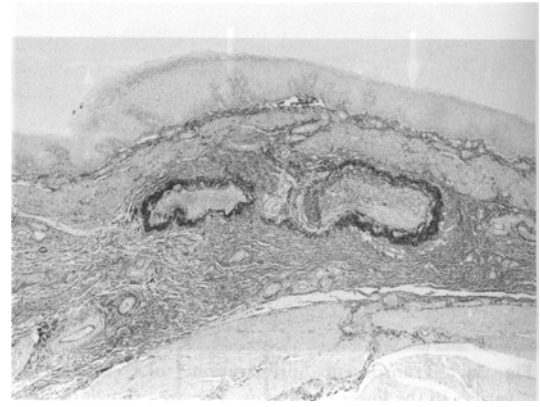

Fig. 6. Case no. 24. Submucosal veins in the area of main trunks are organized with elastosis. (EVG, ×20)

revealed the extensive organized thrombi in both Venetian blind-like veins and four main trunks of varices with elastosis in submucosa (**Fig. 6**).

Case 25. This 60-year-old man had been followed up at the outpatient department since December 1979, because of alcoholic liver disease, and was found to have multiple hepatocellular carcinomas (HCC) by abdominal ultrasonogram in March 1982. He first entered the hospital to receive one-shot chemotherapy for HCC in April 1982. Five months later, he was readmitted because of hematemesis from esophageal varices. During admission, he suffered

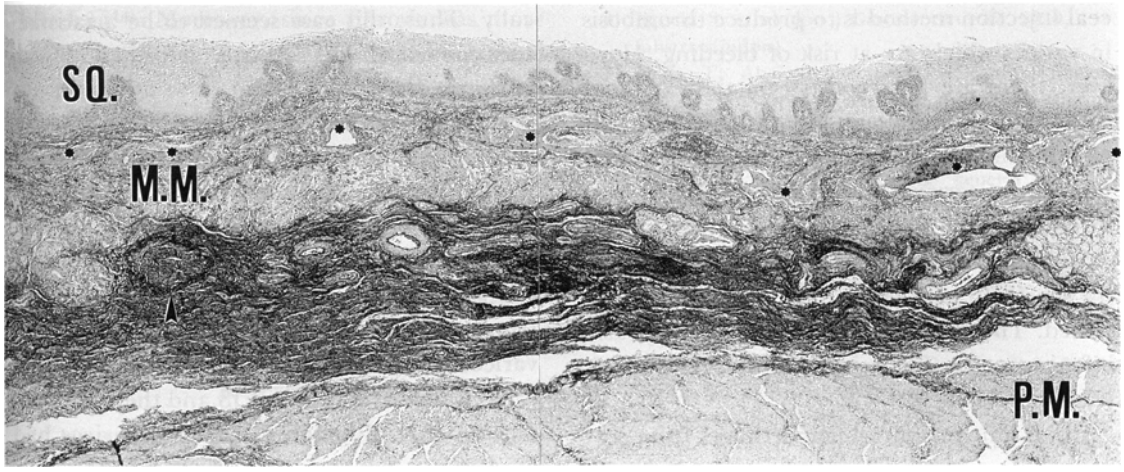

Fig. 7. Case no. 26. Specimen in the area of main trunks. The veins in the lamina propria are dilated and not thrombosed (*). Arrow head shows organized veins with elastosis. Fibrosis is more severe in the submucosa than in the lamina propria. SQ.: squamous epithelium, M.M.: muscularis mucosa, P.M.: proper muscle. (EVG, ×20)

further bleeding, which was stopped only by using a Sengstaken-Blakemore tube. He entered the hospital for the third time on December 31, 1983 because of hematemesis. Endoscopy disclosed varices of a marked degree (Cb, F3) with so-called "red-color sign"[8]. EIS was carried out for the fifth time in five months. The degree of varices improved significantly (Cw, F1) but the red-color signs remained until 22 August, 1984. He subsequently entered the hospital four times after developing fever. The patient died of hemorrhagic gastritis and liver failure on 11 November, 1984. Histopathologically, organized thrombi in the varices were not observed in Venetian blind-like veins but in four main trunks. Softex photograph also revealed no formation of thrombi in Venetian blind-like veins.

Case 26. A 57-year-old man with liver cirrhosis since 1977 first came to the hospital in May 1983. On admission, he was found to have HCC by an abdominal ultrasonogram, and endoscopy demonstrated marked esophageal varices (Cb, F3) with red-color signs. In addition to transcatheter arterial embolization (TAE) for HCC, EIS was performed six times over 6 months. Varices improved significantly after injections (Cw, F1) and red-color signs disappeared. Because of enlargement of HCC and increased alpha-fetoprotein levels, he was readmitted in June 1984, and TAE was repeated. Endoscopy showed no noticeable changes of esophageal varices. He entered hospital for the third time on 8 January, 1985 because of abdominal distension, and reappearance of varices (Cb, F2) was found with red-color signs. The patient eventually died from hemorrhagic gastritis and liver failure on 18 January. Pathological findings in the esophagus demonstrated the organized and shrunk main trunks and submucosal Venetian blink-like veins with elastosis in submucosa. However, the varicose veins in the lamina propria were dilated and not thrombotic, with no elastosis (**Fig. 7**).

Discussion

The main purpose of EIS using the intravari-

ceal injection method is to produce thrombosis in varices which are at risk of bleeding. However, there are few reports[2] on the extent of thrombi in the esophagus following EIS. In this paper, the planar extent of thrombi in the short-term survival cases and the extent of thrombi on the basis of the angioarchitectural characteristics of varices reported by Noda[7] in the short and long-term survival cases were presented. The results obtained may serve as basic information on EIS using the intravariceal injection method.

EIS is able to control hemorrhages from esophageal varices and prolongs survival[3-5,9-11]. However, reappearance of varices or recurrent bleeding after treatment has been reported occasionally because of the increased number of long-term follow-up cases. MacDougall et al.[3] reported that out of 42 patients who survived to continue in the trial after obliteration of varices, 15 required further courses of sclerotherapy because varices reappeared within 6-25 months (mean 9 months), but only 2 of these patients presented with further episodes of bleeding 8 and 13 months after initial obliteration. Makuuchi et al.[2] described that low grade varices recurred in 4.7% of long-term follow-up cases after six months and only 8.9% after 12 months. Ikeda et al.[3] stated that the recurrence rate of varices within a year after esophageal transection surgery was 5.3% (4/75) in contrast to 37.5% (6/16) after EIS ($p<0.001$). If reinjection is carried out at least when recurrence of varices occurs, the mechanism of recurrence seems to be a problem that should be solved. In order to discuss the mechanism of recurrence of varices following EIS, 3 cases among the long-term survival cases were chosen and presented.

In case 24 included by Group 3, esophageal varices were eradicated endoscopically and four main trunks and Venetian blind-like veins were mostly organized and shrunk pathologically. Thus, this case seemed to be a satisfactory one out of the cases in which EIS had been performed.

Although in case 25 included by Group 1, there were no thrombi in the Venetian blind-like veins but in the main trunks, endoscopy revealed the varices to be mostly eradicated. This may be the reason why the varices observed endoscopically generally consisted of four main trunks. We examined 34 cases with esophageal varices in whom portography had been performed before and after EIS and the results indicated that although esophageal varices had all disappeared, two without thrombosis in the Venetian blind-like veins among the 27 cases had early recurrence of the varices[6]. From these data, it is possible to deduce that this case would have had a high possibility of early recurrence.

In case 26, the varices improved significantly after six injections over 6 months, followed by recurrence of the varices 16 months after the first injection. This case therefore seems to be important for discussion of the mechanism of recurrence. Pathologically, four main trunks and submucosal Venetian blind-like veins were shrunk and organized, but the subepithelial veins were dilated and not thrombotic, with no elastosis. Although the varices observed endoscopically generally consisted of four main trunks, in this case the varices as well as the so-called "red-color sign" appeared to be formed from dilated subepithelial veins. The recurrent varices, furthermore, seemed to have arisen from the untreated veins, because the veins which had been occluded by red thrombi were organized with elastosis[1]. The not-thrombotic Venetain blind-like veins in the lamina propria shown in Group 2 might have led to not only the recurrence of the varices observed endoscopically but also to the reappearance of the red-color sign which is caused by dilatation of the subepithelial veins[12,13], showing a risk of

bleeding[14]. Moreover, since fibrosis was more severe in the submucosa than in the lamina propria, the veins might have been converted into varices in a relatively short time.

Pathologically, it seems to be ideal to produce thrombosis not only in the main trunks but also in the Venetian blind-like veins. In order to produce a thrombosis of this extent and to prevent the recurrence of varices after eradication, a further device may be necessary.

References

1) Matsumoto S: Clinicopathological study of sclerotherapy of esophageal varices. I. A review of 26 autopsy cases. Gastroenterol Jpn 21: 99, 1986
2) Evans DMD, et al: Oesophageal varices treated by sclerotherapy: a histopathological study. Gut 23: 615, 1982
3) MacDougal BRD, et al: Increased long-term survival in variceal haemorrhage using injection sclerotherapy. Results of a controlled trial. Lancet 1: 124, 1982
4) Makuuchi H, et al: Endoscopic sclerothrombotherapy for esophageal varices. Technique and long term follow-up of ETP method. I to Cho 20: 497, 1985 (Jpn)
5) Ikeda K, et al: Effect of endoscopic injection scleroembolization therapy for esophageal varices (comparison with effect of esophageal transection surgery). Gastroenterol Endosc 27: 2376, 1985 (Jpn)
6) Eguchi S, et al: Jpn J Gastroenterol 82: 2239, 1985 (abstract in Jpn)
7) Noda T: Angioarchitectural study of esophageal varices. With special reference to variceal rupture. Virchows Arch (Pathol Anat) 404: 381, 1984
8) Japanese Research Society for Portal Hypertension (Chairman: Inokuchi K): The general rules for recording endoscopic findings on esophageal varices. Jpn J Surg 10: 84, 1980
9) Johnston GW, et al: A review of 15 years' experience in the use of sclerotherapy in the control of acute haemorrhage from oesophageal varices. Br J Surg 60: 797, 1973
10) Takase Y, et al: Injection sclerotherapy of esophageal varices for patients undergoing emergency and elective surgery. Surgery 92: 474, 1982
11) Clark AW, et al: Prospective controlled trial of injection sclerotherapy in patients with cirrhosis and recent variceal hemorrhage. Lancet 2: 552, 1980
12) Nakamura Y: Histopathological and endoscopic studies on esophageal varices with special reference to "red-color sign". Gastroenterol Endosc 27: 17, 1985 (Jpn)
13) Arakawa M, et al: Clinicopathological studies of esophageal varices. Histopathological findings of ruptured esophageal varices and its relationship to endoscopical findings. Gastroenterol Endosc 27: 191, 1985 (Jpn)
14) Beppu K, et al: Clinicopathological studies of esophageal hemorrhage by esophageal endoscopy. Gastrointest Endosc 27: 213, 1981