Virchows Archiv A Pathol Anat (1991) 418:169–174

Virchows Archiv A
Pathological Anatomy and Histopathology

Focal veno-occlusive lesions following metastasis of cancer in the liver with special reference to obstruction of lymphatics in hepatic veins

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Received July 23, 1990 / Accepted October 2, 1990

Summary. Focal veno-occlusive lesions and congestion of the liver are found frequently at autopsy in patients with metastatic carcinoma in the liver. In 6 cases, intimal proliferation of loose connective tissue with dilatation of lymphatic capillaries was seen continuously from the terminal hepatic venule to the hepatic vein, and cancer cells were found only in lymphatic capillaries in the wall of the hepatic vein. In 7 cases, cancer cells infiltrated directly into the adventitia of the sublobular vein and intimal proliferation of loose connective tissue with or without formation of recent thrombi was observed. A main causative factor of hepatic veno-occlusive disease is thought to be leakage of plasma due to endothelial injury to the terminal hepatic venule and sublobular vein. Lymphatic obstruction, in addition to a direct reaction to invasion of cancer cells to the vessel wall, may also cause veno-occlusive lesions due to stasis and leakage of lymph fluid into the intima of the terminal hepatic venule, sublobular vein and hepatic vein.

Key words: Hepatic veno-occlusive disease – Focal veno-occlusive lesion – Lymphatic obstruction – Metastatic carcinoma in liver

Introduction

Veno-occlusive disease of the liver is characterized histologically by a progressive and concentric non-thrombotic occlusion of the lumina of the terminal hepatic venule and sublobular vein. This is due to intimal proliferation of loose connective tissue with congestion, haemorrhage and necrosis of hepatocytes in the centrilobular area. It is known that veno-occlusive disease of the liver may be induced by many factors, such as hepatotoxic pyrrolizidine alkaloids (Bras et al. 1954; Stein and Isaacson 1962; Stillman et al. 1977), irradiation (Scott et al. 1962; Reed and Cox 1966; Fajardo and Colby 1980), and antineoplastic and immunosuppressive agents (Marubbio and Danielson 1975; Griner et al. 1976; Shulman et al. 1980; Gottfried and Sudilovsky 1982). It is usual that the entire liver is involved and for ascites and hepatomegaly to occur. A similar veno-occlusive lesion is found frequently in sections of the liver taken at autopsy from patients with metastatic carcinoma in the liver, although the lesions are focal. In some such cases, lymphatic obstruction by the infiltrating cancer cells is seen in the wall of the hepatic vein. It is possible that stasis and leakage of lymph fluid following the lymphatic obstruction stimulate the ingrowth of loose connective tissue in the intima, since veno-occlusive disease is thought to be caused by leakage of plasma due to injury to the endothelium (Bras et al. 1954; Marubbio and Danielson 1975; Griner et al. 1976; Fajardo and Colby 1980; Shulman et al. 1980). The present study was undertaken to clarify whether lymphatic obstruction relates to the mechanism for the development of veno-occlusive lesions.

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Materials and methods

Cases with non-cirrhotic liver containing metastatic carcinoma and focal veno-occlusive lesions were selected from 800 consecutive autopsies from Osaka Medical College Hospital. Thirteen were chosen. Liver slices (3 mm in width) across the hepatic vein branches were obtained serially from congested areas and the sublobular and hepatic veins distal to the congested areas. These specimens were fixed in 10% neutral formalin and embedded in paraffin. Some histological sections of each liver slice were stained with haematoxylin and eosin, Masson's trichrome method, Gomori's method for reticulum and van Gieson's method for elastic fibres. Serial histological sections of liver slices were examined when necessary.

For comparison with the focal veno-occlusive lesions in patients with metastatic carcinoma in the liver, a case with veno-occlusive disease due to mitomycin C, a liver abscess and a case of cirrhosis (HBsAg, positive) were selected from autopsies performed at Osaka Medical College Hospital.

Table 1. Clinical data, gross autopsy findings and treatment of patients

	Age (years)	Sex	Primary adenocarcinoma/ diagnosis	Liver weight (g)	Congestion	Ascites (ml)	Carcinomatosis peritonei	Therapeutic regimen
Group 1								
Case 1	61	Male	Colon	3340	Moderate	3000	No	Mitomycin C, fluorouracil
Case 2	83	Male	Stomach	2030	Severe	3000	No	
Case 3	64	Male	Stomach	1360	Moderate	6000	Yes	Fluorouracil
Case 4	70	Male	Stomach	2510	Slight	1900	No	
Case 5	73	Male	Stomach	2950	Moderate	4500	No	Mitomycin C
Case 6	79	Male	Colon	2320	Slight	3400	Yes	Mitomycin C
Group 2								
Case 7	58	Female	Stomach	1200	Minimal	1500	No	Mitomycin C, fluorouracil
Case 8	77	Female	Lung	1120	Minimal	0	No	
Case 9	36	Male	Lung	2160	Slight	0	No	Mitomycin C, vincristine,
Case 10	56	Male	Pancreas	2000	Slight	3000	Yes	Tegafur
Case 11	50	Female	Stomach	2400	Minimal	1400	Yes	Mitomycin C
Case 12	78	Male	Lung	1150	Slight	2500	Yes	Mitomycin C
Case 13	46	Male	Pancreas	2290	Slight	2000	Yes	
Group 3								
Case 14	39	Female	Veno-occlusive disease	1280	Severe	2000	No	Mitomycin C
Case 15	54	Female	Liver abscess	1690	Moderate	1800	No	
Case 16	46	Male	Liver cirrhosis	1550	Minimal	2200	No	

Results

The clinical data and gross autopsy findings and treatments of patients are shown in Table 1. No patient was given irradiation or immunosuppressive therapy.

The cases were divided into three groups as follows: group 1, the 6 cases with a distance between congestive area and cancer nodules; group 2, the 7 cases with congestive area adjacent to cancer nodules; group 3, the 3 cases selected for comparison with group 1 and group 2.

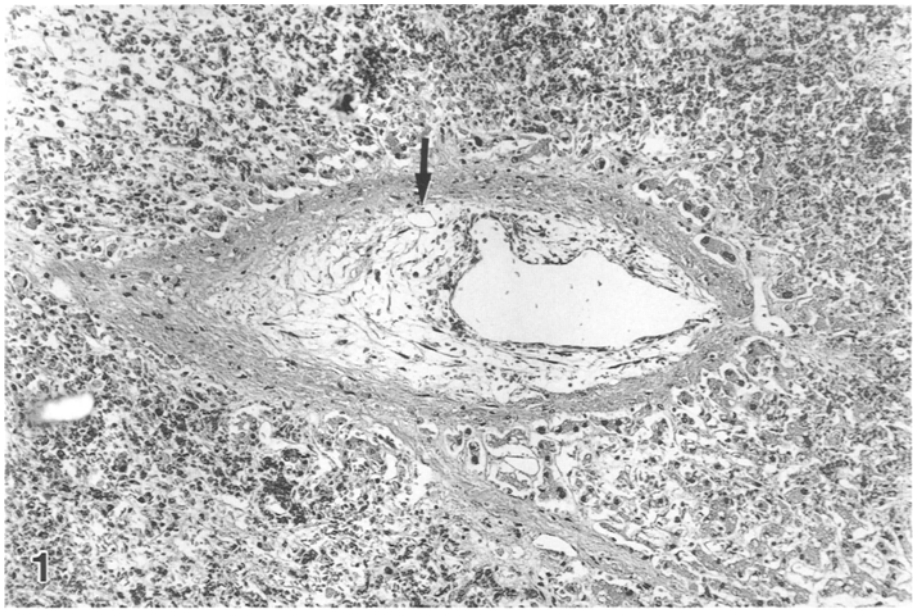
In group 1 (cases 1–6), intimal proliferation of loose connective tissue with dilatation of lymphatic capillaries and lymphatic capillary-like spaces (vessels containing no erythrocytes, irrespective of the presence of endothelial cells) was seen continuously from the terminal hepatic venule to the hepatic vein (Fig. 1). Cancer cells were found in and around lymphatics of the wall of the hepatic vein, that is to say, in the distal portion of the affected vessels (Fig. 2), but not in or around the upstream vessels. No evidence of severe inflammation was seen around the affected veins.

In group 2 (cases 7–13), cancer nodules compressed the sublobular vein and narrowed their lumina. Intimal proliferation of loose connective tissue was not found in the narrowed vessels or in the downstream vessels, when cancer cells did not invade into the vessel wall. In contrast to this, when cancer cells infiltrated directly into the wall, at least the adventitia of the vessel, loose connective tissue proliferated in the intima (Fig. 3). Recent thrombi and proliferation of loose connective tissue around them were often seen in the lumen of the vessel invaded by cancer cells (Fig. 4). In the proliferated loose connective tissue in the intima, small blood vessels were frequently seen, but the presence of lymphatic vessel or lymphatic capillary-like space was not evident. There was no evidence of severe inflammation around the affected vessels. The degree of congestion of the liver and of ascites was more prominent in group 1 than in group 2.

In group 3, severe centrilobular and mid-zonal congestion and haemorrhage were found in the entire liver in a patient treated with mitomycin C (case 14). Proliferation of loose connective tissue with small blood vessels, lymphatic capillaries and lymphatic capillary-like spaces and extravasation of erythrocytes were seen diffusely in the intima of the terminal hepatic venule, sublobular vein and hepatic vein (Fig. 5). In a case with liver abscess (case 15), neutrophils, macrophages and lymphocytes infiltrated around the walls of the sublobular veins, and loose connective tissue proliferated in their lumina (Fig. 6). In the proliferated loose connective tissue, blood capillaries and extravasation of erythrocytes were found, but the presence of lymphatic capillaries was not clear. In a patient with liver cirrhosis (case 16), proliferation of loose connective tissue with lymphatic capillaries and lymphatic capillary-like spaces was found sporadically in the intima of the peripheral branches of the hepatic vein in connective tissue septa (Fig. 7).

Discussion

A number of hypotheses have been proposed on the pathogenesis of veno-occlusive disease and focal veno-



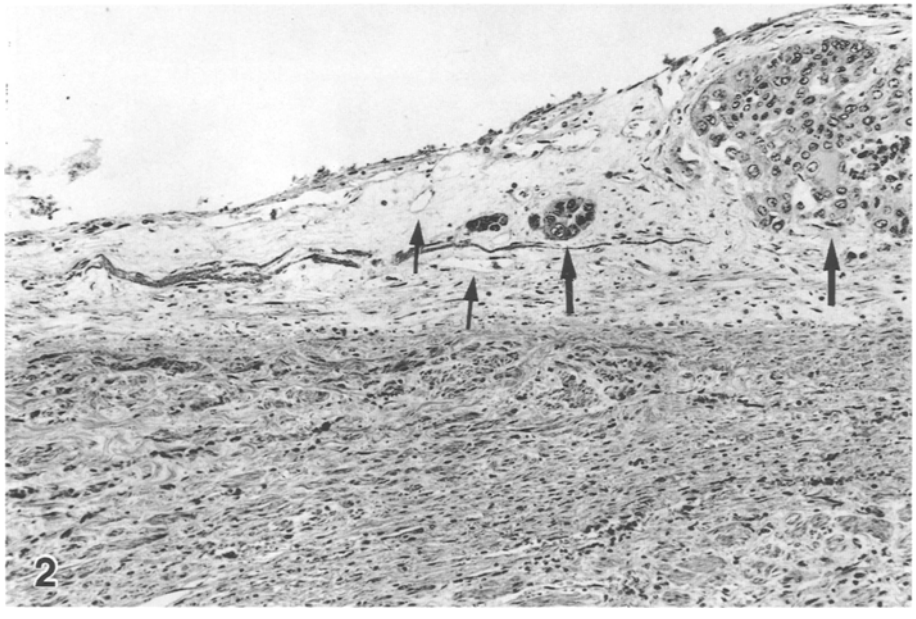


Fig. 1. Case 5. The lumen of the sublobular vein is narrowed by intimal proliferation of loose connective tissue with dilatation of lymphatic capillary (*arrow*). Congestion and haemorrhage are evident around the injured vein. There is no cancer cell. Haematoxylin and eosin (H&E), ×100

Fig. 2. Case 5. Cancer cells in and around lymphatics (*large arrows*) and dilatated lymphatic capillaries (*small arrows*) in the intima with proliferation of loose connective tissue are seen in the hepatic vein. H&E, ×100

occlusive lesions. The first is that veno-occlusive disease may result from leakage of plasma and extravasation of erythrocytes in the intima due to injury to the endothelium of the terminal hepatic venule, sublobular vein and hepatic vein. This may be produced by pyrrolizidine alkaloids, irradiation, and antineoplastic and immunosuppressive agents (Bras et al. 1954; Marubbio and Danielson 1975; Griner et al. 1976; Asbury et al. 1980; Fajardo and Colby 1980; Shulman et al. 1980; McIntyre et al. 1981; Gottfried and Sudilovsky 1982). In such veno-occlusive disease, veno-occlusive lesions are usually seen in the entire liver. In contrast to this, veno-occlusive lesions in the liver with metastatic carcinoma were seen only focally in the present study although morphologically similar to those of veno-occlusive disease. Moreover, the identical lesions were also seen in livers with metastatic carcinoma in patients that had not received antineoplastic drugs, irradiation or immunosuppressive agents. This may suggest that the veno-occlusive lesions in the liver with metastatic carcinoma could be induced by some localized injury other than antineoplastic agents.

Secondly, it is proposed that obliteration and stenosis of the hepatic vein branches in liver cirrhosis is due to phlebosclerosis and compression by regenerative nodules. These reduce blood to be delivered to vessels distal to the injured veins, and the reduced blood flow stimulates intimal proliferation to decrease the calibre of vessels to a size appropriate for the amount of blood (Goodman and Ishak 1982; Nakanuma et al. 1985). However, there was no obstructive lesion in the upstream vessels of the veins with veno-occlusive lesions in livers with metastatic carcinoma in the present study.

Thirdly, it is known that veno-occlusive lesions may

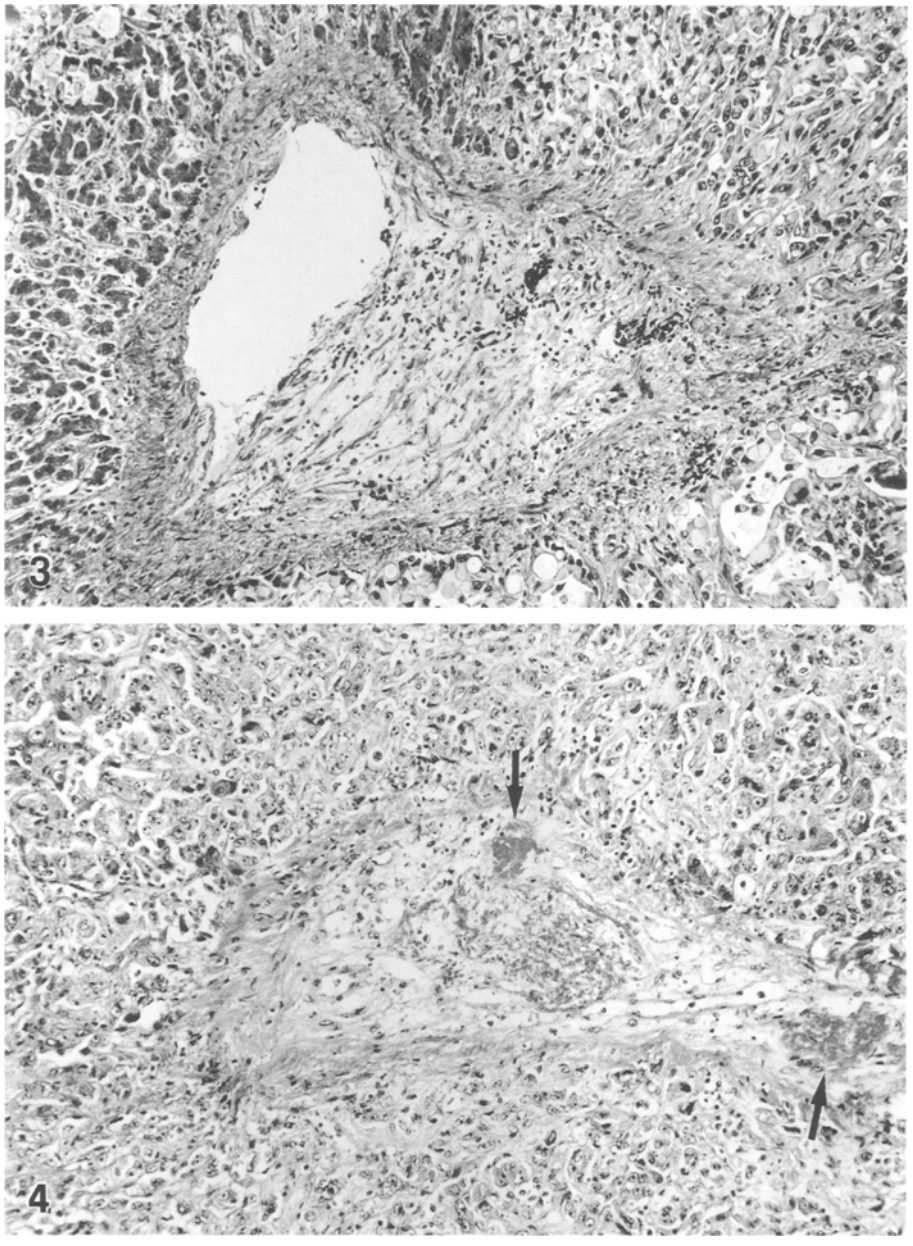


Fig. 3. Case 11. Cancer cells infiltrate directly into the adventitia of the sublobular vein, and loose connective tissue proliferates in only the intima of the portion with the injured adventitia. H&E, ×100

Fig. 4. Case 9. Invasion of cancer cells to the adventitia of the sublobular vein, fibrin thrombi (*arrows*) and proliferation of loose connective tissue in the intima are seen. H&E, ×100

be induced as a reaction to severe inflammation (Goodman and Ishak 1982). In the present study, veno-occlusive lesions were found in the sublobular veins that drain abscess in the case with liver abscess. However, it is believed that causes other than a reaction to inflammation probably play a role in the development of veno-occlusive lesions in patients with metastatic carcinoma in the present study, since there was no severe inflammation of the liver.

We would like to propose the hypothesis that at least some veno-occlusive lesions in patients with metastatic carcinoma in the liver may result from lymphatic obstruction of the wall of the sublobular and hepatic vein. It is known that the lymphatics accompanying the terminal hepatic venule, sublobular vein and hepatic vein originate in their subendothelial connective tissue, form an abundant lymphatic network, penetrate the media and then continue into the network of lymphatics having valves in the adventitia: most of them connect with the lymphatics of the diaphragm without increasing in size or forming collecting vessels (Magari 1990). Moreover, the lymphatic capillaries which originate in the closely interwoven bundles in the subendothelial connective tissue of the hepatic vein branches, are not surrounded by endothelial cells. Accordingly, when cancer cells obstruct the lymphatics of the wall of the sublobular and hepatic vein due to embolism or direct invasion, stasis and leakage of lymph fluid in the intima may occur easily and subsequently may stimulate ingrowth of loose connective tissue.

Lymphatic obstruction by cancer cells can explain the occurrence of veno-occlusive lesions in the present study, particularly in the cases with a distance between the affected vessels and cancer nodules, although it can-

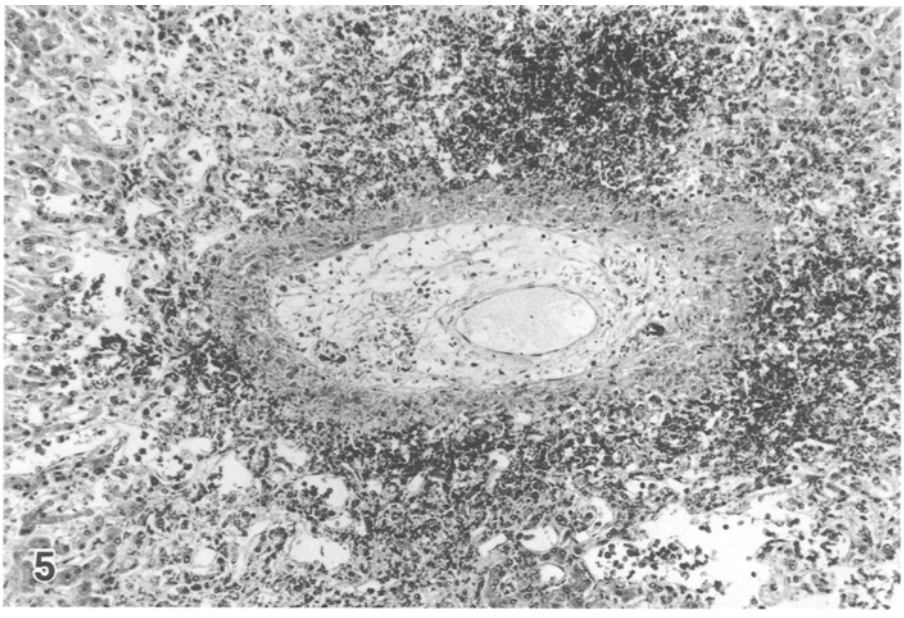


Fig. 5. Case 14. Proliferation of loose connective tissue with lymphatic capillaries and lymphatic capillary-like spaces in the intima of the sublobular vein and concentric narrowing of the lumen are seen. Sinusoidal dilatation, congestion and haemorrhage are prominent in the lobules. H&E, ×100

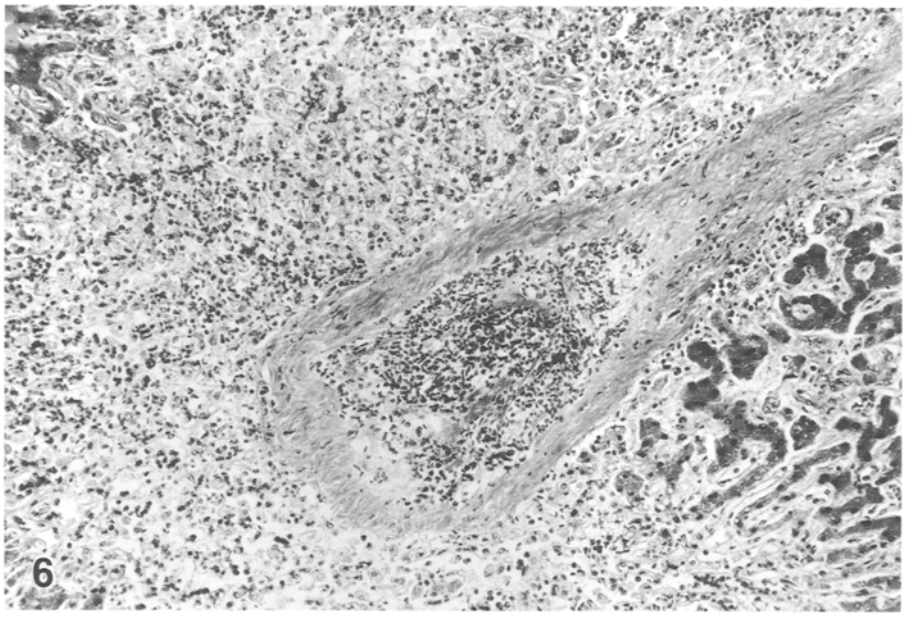


Fig. 6. Case 15. Extravasation of erythrocytes and proliferation of loose connective tissue are found in the intima of the sublobular vein surrounding neutrophils, macrophages and lymphocytes. H&E, ×100

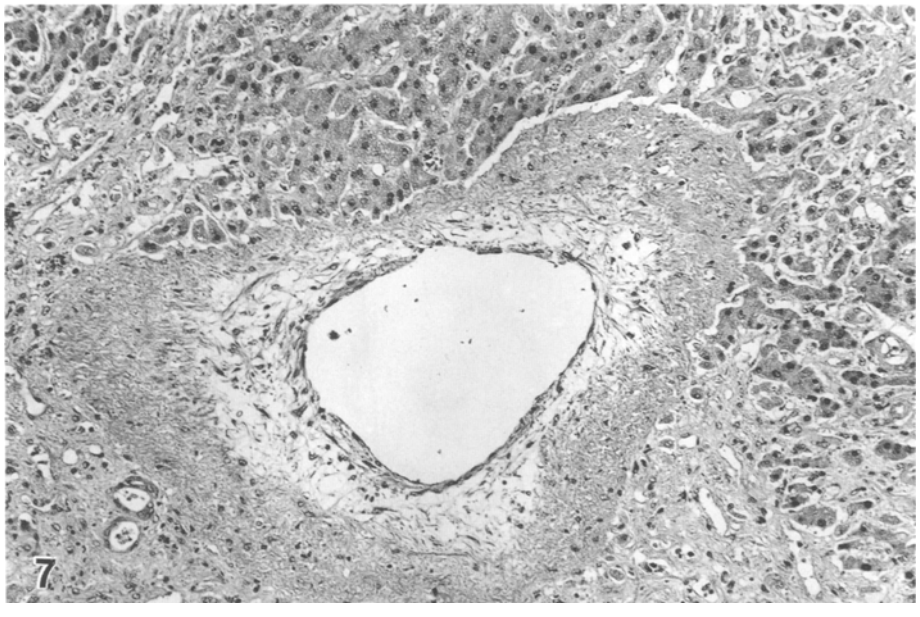


Fig. 7. Case 16. Proliferation of loose connective tissue with lymphatic capillaries and lymphatic capillary-like spaces is seen in the intima of the hepatic vein branch. H&E, ×100

not be entirely denied that the lymphatic obstruction is a consequence of veno-occlusive disease. Furthermore, it is speculated that veno-occlusive lesions in liver cirrhosis are also caused by the lymphatic obstruction, in addition to a reaction to the reduced blood flow. Not only hepatic vein branches but also lymphatics in their walls are damaged and disturb the flow, following an irreversible alteration of the lobular architecture, and compression by regenerative nodules and proliferated connective tissue. However, a direct reaction to infiltration of cancer cells and inflammatory cells to the vessel wall seems more likely to play a role in the development of the veno-occlusive lesions adjacent to cancer nodules and liver abscesses.

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