A Scanning Electron Microscopic Study of Subcapsular Lymphatic Capillaries of the Normal Liver and the Liver in Budd-Chiari Syndrome after Chemical Digestion

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ABSTRACT. The subcapsular lymphatic capillaries of normal and Budd-Chiari syndrome livers were observed by scanning electron microscopy after manual stripping of the liver capsule followed by chemical digestion (HCl-collagenase). The following results were obtained.

1. The stereoscopic architecture and external surfaces of the subcapsular lymphatic capillaries of the normal liver and the liver in Budd-Chiari syndrome were clarified.
2. In the normal liver, the subcapsular lymphatic capillaries were divided into the following three types: Type-1, initial lymphatics with many small pores, spreading in a fine mesh just above the hepatic parenchyma; Type-2, lymphatic capillaries with many blind-ended porous branches, running stereoscopically in all directions, and Type-3, aggregate vessels of the subcapsular lymphatic capillaries showing a relatively straight and long running course. The initial lymphatics were considered to be peculiar to the liver for absorption and drainage of its abundant lymph containing a large quantity of protein.
3. In Budd-Chiari syndrome, the subcapsular lymphatic capillaries were anastomosed and crossed one another, and had blind-ended branches. On their surface, larger pores than those in the normal liver were observed. These large pores were considered to be suitable for draining of the increased hepatic lymph of this syndrome.

Key words: hepatic lymphatic capillary — initial lymphatics — Budd-Chiari syndrome — scanning electron microscopy — chemical digestion method

In comparison with the lymph of other organs and tissues, hepatic lymph has two distinct characteristics. One is its large quantity, accounting for as much as 25-50 per cent of the lymph flow volume in the thoracic duct,[1] and the other is its high protein content, constituting approximately 80 per cent of plasma protein.[2] These phenomena are produced by a high blood flow through the liver and characteristic parenchymal microcirculation through the highly permeable sinusoid.[3] A major source of hepatic lymph is the perisinusoidal space of Disse, and the lymph is removed from the interstitial tissues by lymph vessels.[4]

There have been very few morphological studies of the hepatic lymphatics.

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Consequently, their fine morphological features have not been adequately characterized.[5,6] The fine morphology of the hepatic lymph capillaries has been investigated only by transmission electron microscopy (TEM),[7-9] and scanning electron microscopy (SEM) by the injection method.[10] In our department, Tokumitsu S. proposed using the chemical digestion method with SEM for study of the lymph capillaries.[11] The initial hepatic lymphatics, in particular their three-dimensional microstructures, have not yet been clarified in the normal human liver or in Budd-Chiari syndrome livers.[3,12,13]

SEM observation of biological specimens using chemical digestion allows wide-ranging stereoscopic observation of the architectures and structures embedded in connective tissue and also of their external surface.[14] Hepatic subcapsular lymphatics are abundant.[15] The author extended the Tokumitsu study to observe the stereoscopic architecture and external surfaces of hepatic subcapsular lymph capillaries in detail, employing the Kobayashi method,[16] in which chemical digestion is applied following manual stripping of the liver capsule.

The hepatic capsule generally includes both the serosa; i.e., the serosal mesothelium, and the connective tissue (Glisson's capsule) attached to the serosa.[5,6] In the present study, when the capsule was stripped manually it was stripped at various layers ranging from the center to deep sites of the subserosal connective tissue.

MATERIALS AND METHODS

1. Materials

The materials were three normal livers removed at autopsy and surgically biopsied liver specimens of a patient with a definitive diagnosis of Budd-Chiari syndrome. The three autopsied specimens were normal macroscopically and light microscopically. The histological findings of the surgically biopsied specimens were consistent with those of Budd-Chiari syndrome.

2. Methods

Small tissue slices (5×5×4 mm) including the liver capsule were prepared from the autopsied livers and the biopsied liver blocks, and were fixed in a phosphate buffer containing 2 per cent glutaraldehyde for 72 hours. Then they were washed with a 0.1 M phosphate buffer solution. After manual stripping of the hepatic capsule with a pincette, the specimens were immersed in 6N HCl at 60°C for 60 minutes. Next they were washed with the same buffer solution, and then immersed in a phosphate buffer solution containing 10 mg of Sigma type I collagenase per 10 ml at 37°C for 6-12 hours for digestion. Washing with distilled water was followed by dehydration with an ethanol series, immersion in isoamyl acetate, critical point drying, gold sputter coating, and observation with a JSM-T300 Type scanning electron microscope at an accelerated voltage of 10-15 Kv.

For light microscopy, the specimens were fixed in 10 per cent formalin solution and embedded in paraffin. The thin sections were stained separately with HE and Azan.

RESULTS

1) Light microscopic observations

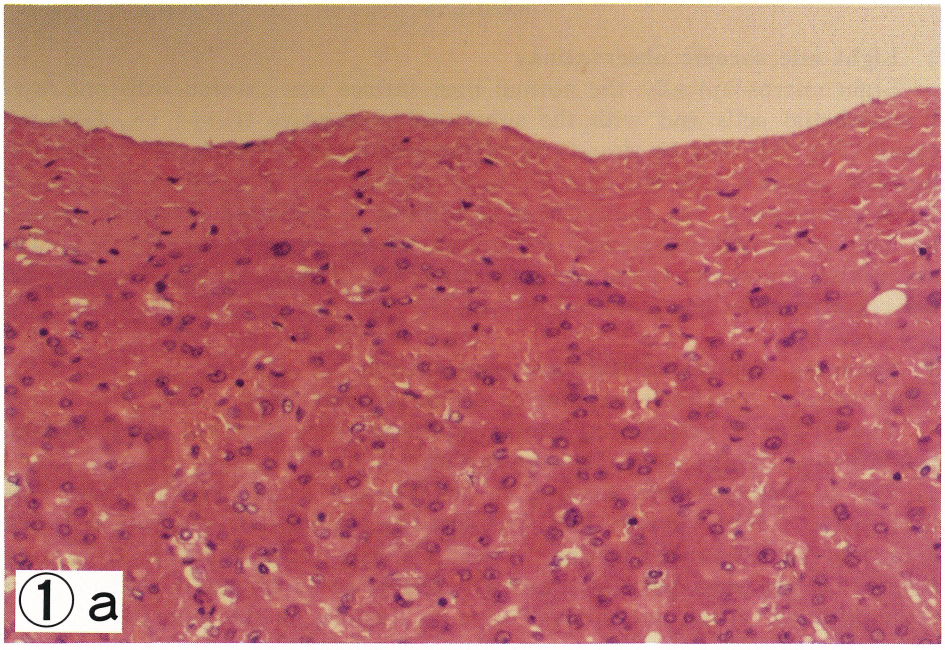
Light microscopically, the normal liver surface was covered with one layer of mesothelial cells and with the subserosal connective tissue; i.e., Glisson's capsule (Fig 1a). Fig 1b shows one of the specimens in which the capsule was manually stripped. In this case, the liver capsule was stripped in the vicinity of the parenchyma. In Budd-Chiari syndrome, a thickened Glisson's capsule and subcapsular fibrosis enclose the nodule of the parenchyma (Fig 1c). The subcapsular connective tissue contains numerous dilated interstitial spaces that may correspond to lymphatics (Fig 1d).

2) Scanning electron microscopic observations

1. Subcapsular lymphatic capillaries of the normal liver

Three types of subcapsular lymph capillaries were observed respectively at three different depths from the liver surface.

Fig 2a shows vessels existing in the deepest areas; i.e., just over the parenchyma. These vessels had fine, net-like, triangular, quadrilateral and pentagonal structures resembling a sheet. They were about 5-10 μm in diameter for the most part, and partially dilated to 15-20 μm in diameter like a cyst (arrows). There are no bile ducts or ductules in the liver capsule with the exception of the portal tracts. The wall of these vessels consisted of a single layer of flat endothelial cells, and had no pericytes. These vessels were neither blood capillary vessels nor bile ducts. They were considered to be the initial lymphatic capillaries forming a network just above the subcapsular parenchyma of the liver. Magnification of these net-like lymphatic capillaries (Fig 2b) revealed many small pores about 0.1-2 μm in diameter irregularly arranged in a tortoise shell pattern mainly conforming to the interendothelial openings on the external surfaces (arrows). There were also small pores gathered together and appeared like a sieve in the endothelial cells (white arrows). Fine fibers connected some parts of the external surfaces with the surrounding net-like connective tissue fibers forming thin bundles (arrowheads). Such thin bundles mainly adhered to the vicinity of the interendothelial openings. These fine fibers were considered to be the anchoring filaments. These lymphatic capillaries were assigned to Type-1.



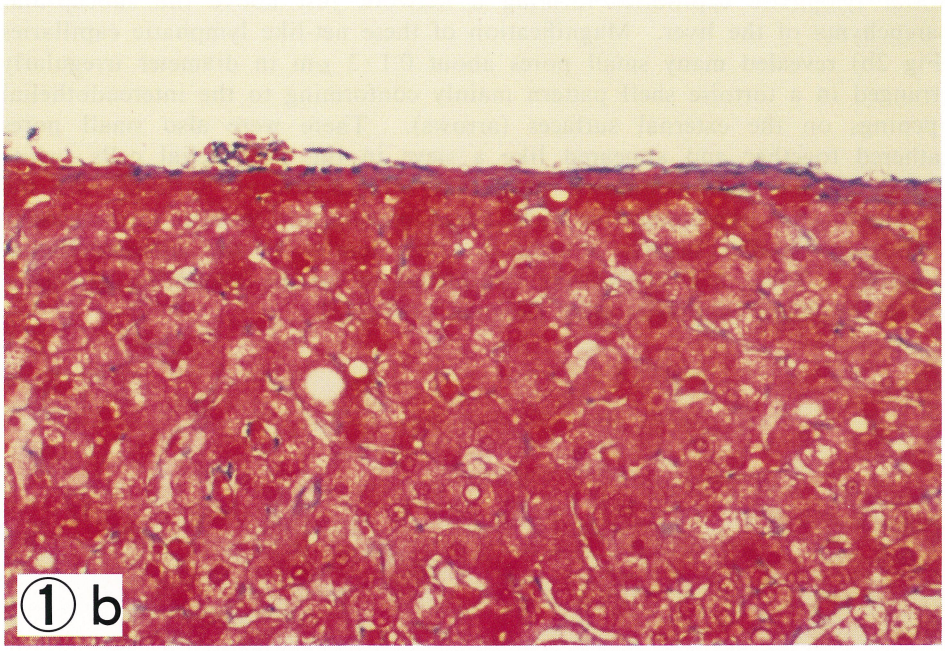
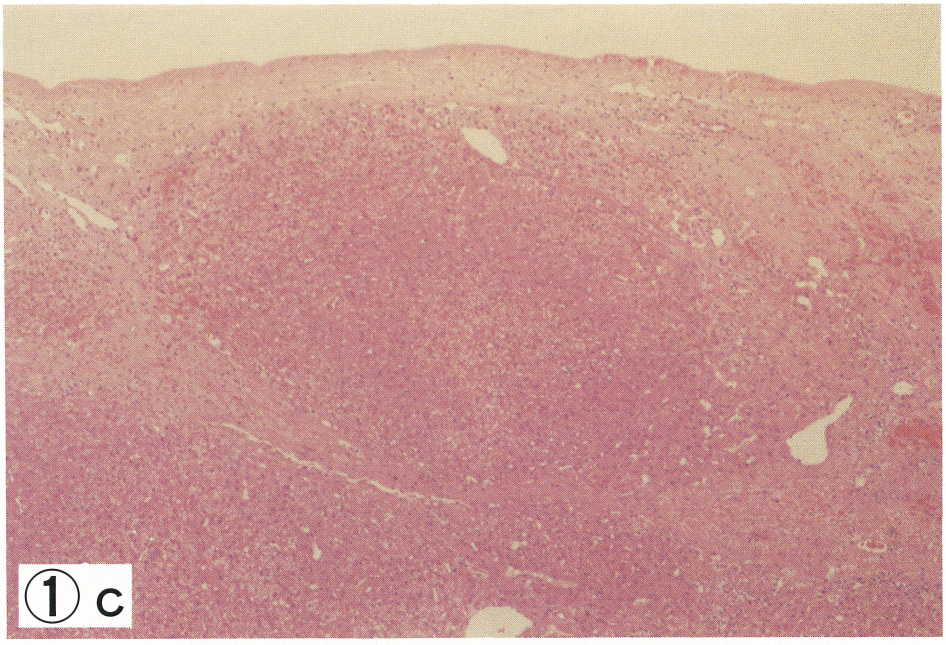


Fig 1a. Light micrograph of normal liver. The liver capsule has two layers consisting of mesothelial cells and connective tissue. (HE× 200)

Fig 1b. The liver capsule is stripped in the vicinity of the parenchyma. (Azan×200)



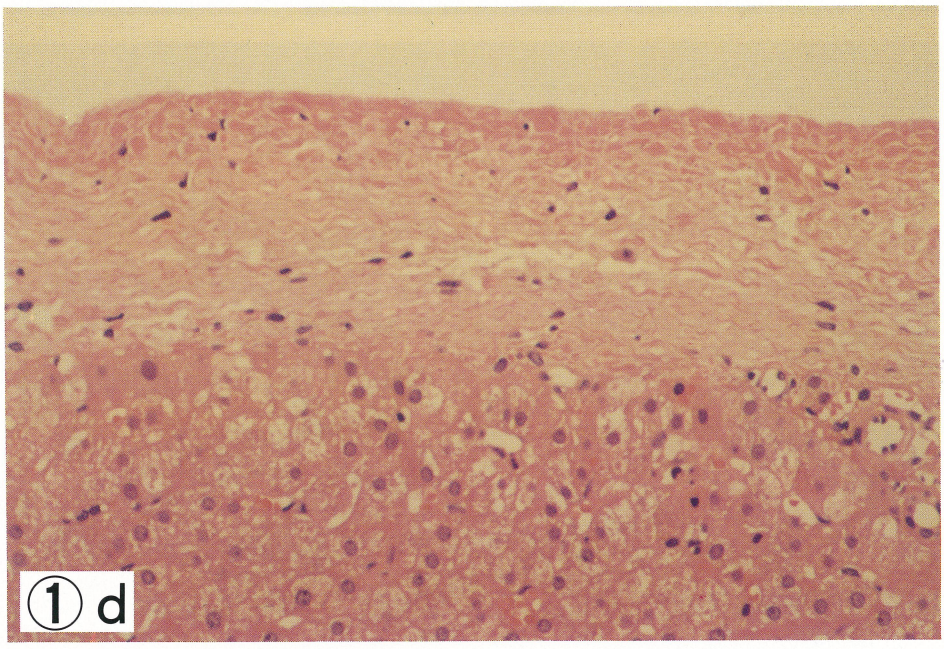
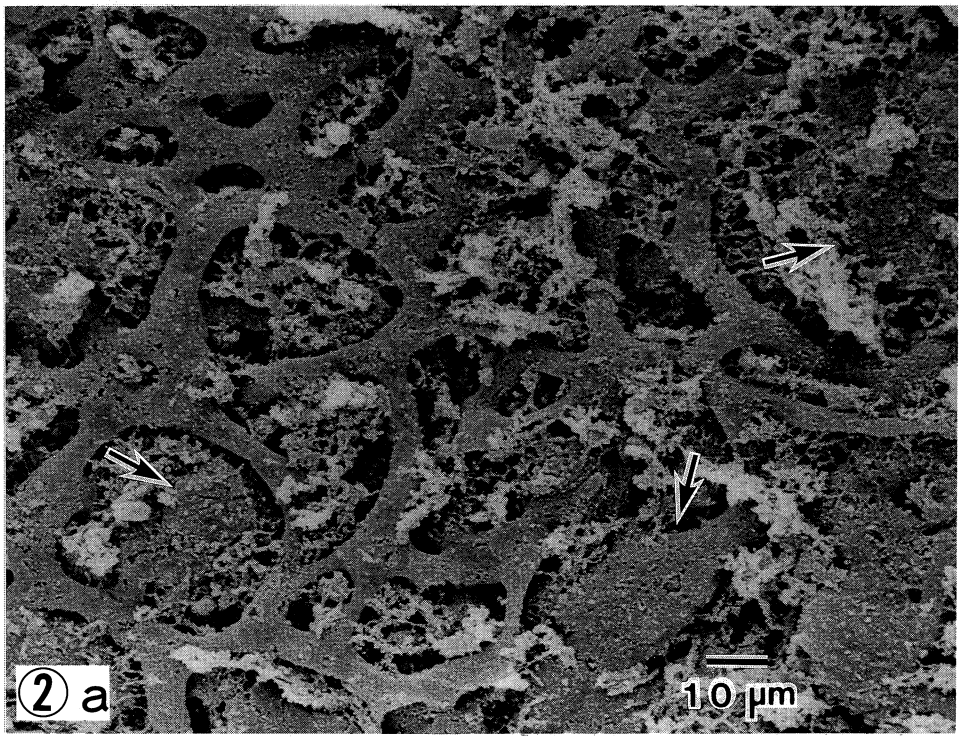


Fig 1c. Light micrograph of Budd-Chiari syndrome. A thickened Glisson's capsule and subcapsular fibrosis enclose a nodule of parenchyma. (HE×40)

Fig 1d. High magnification of part of Fig 1c. The subcapsular connective tissue has thickened and contains numerous dilated interstitial spaces corresponding to lymphatics. (HE×200)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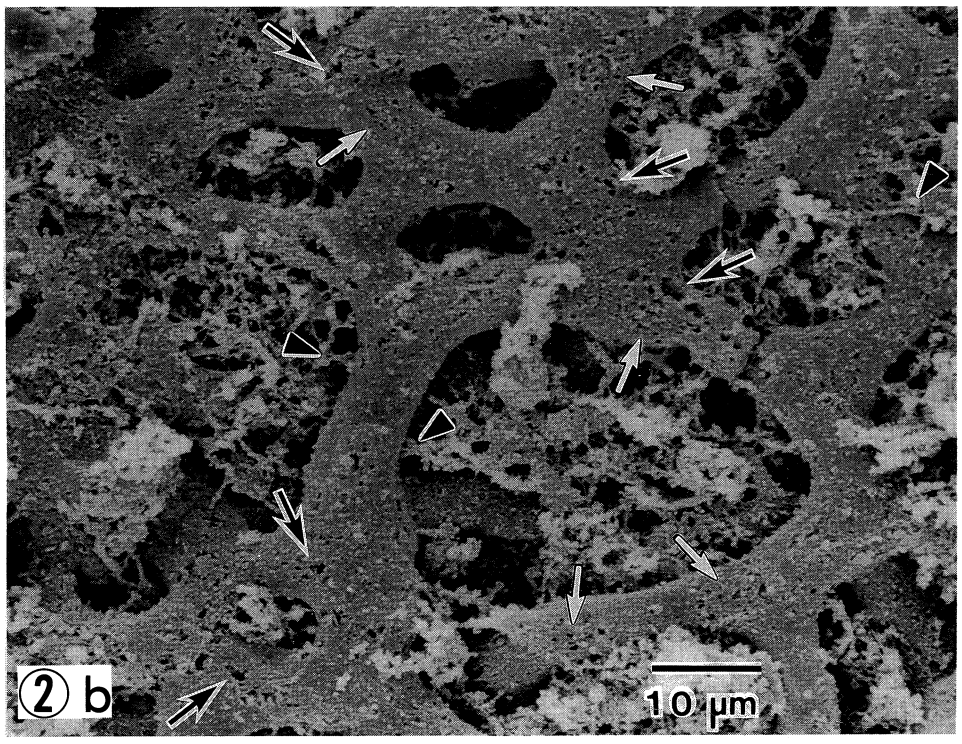
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On specimens in which the capsule was stripped more shallowly than in the above-mentioned specimens, the author observed vessels about 5-10 μm in diameter (Fig 3a). They had polyhedral stereoscopic net-like structure, crossing and anastomosing with one another and obliquely running toward the deep part of the connective tissue. They had many blind-ended branches (arrows). No pericytes were observed. The vessels were found to have a thin flat endothelium from observation of a site where the vessel's wall had been partially broken during preparation of the specimen (Fig 3b). Magnification revealed relatively large pores about 1-2 μm in diameter on the surface existing in interendothelial areas, especially in the blind-ended branches (Fig 3c, arrows). The vessels were also lymphatic capillaries, and were considered to be lymphatic capillaries existing slightly distant from the hepatic parenchyma. Thin fiber bundles considered to be anchoring filaments were also observed (arrowheads). These lymphatic capillaries were assigned to Type-2.

Rather thick (10-15 μm in diameter) lymphatic capillaries which followed a relatively straight and long running course were observed on the specimens where the capsule was stripped most shallowly (Fig 4a). Magnification revealed only a few small pores in interendothelial areas (Fig 4b, arrows). These lymphatic capillaries were assigned to Type-3.

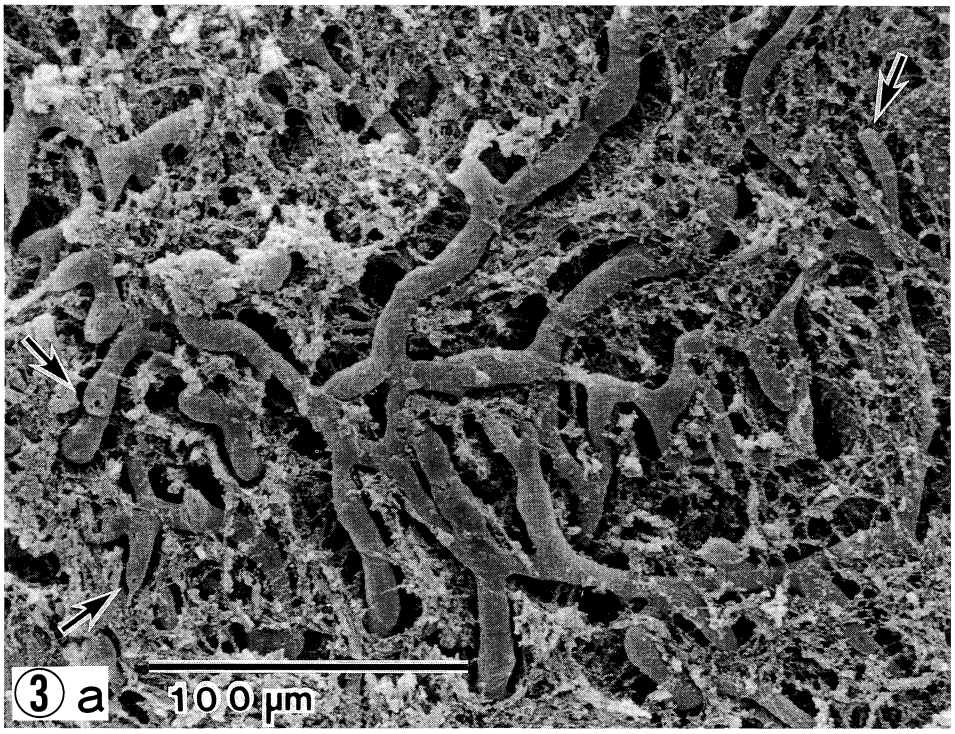
2. Subcapsular lymphatic capillaries of the liver in Budd-Chiari syndrome

SEM observation disclosed smooth-surfaced vessels on the connective tissue fibers escaping digestion (Fig 5). They showed repeated irregular anastomoses and branching (Fig 5a), and had blind-ended branches (Fig 5b, white arrows). The smooth-surfaced vessels varied from about 5 to 10 μm in diameter. No pericytes were observed. The vessels had many pores about 0.1 - 3 μm in diameter on the surface (Fig 5a 5b, arrows), which existed in the interendothelial areas. There were some fibers connecting the vessels with the surrounding connective tissue (Fig 5a, 5b, arrowheads). They were considered to be the subcapsular lymphatic capillaries of the liver in Budd-Chiari syndrome, because of their course, the findings on their external surfaces, which had no pericytes, and the presence of blind-ended branches. The fibers adhering to the vessels were also considered anchoring filaments. No subcapsular lymphatic capillaries similar to the Type - 1 capillaries in the normal liver were observed in this syndrome.

←Fig 2. Type-1 lymphatic capillaries (Initial lymphatics).

2a : SEM after stripping of the liver capsule at the deepest layer, followed by chemical digestion. The Type-1 lymphatic capillaries form a network with dense multanglar meshes. Most of them are flat and between 5 and 10 μm in diameter. Some are partially dilated to 15-20 μm like a cyst (arrows). No pericytes are seen.

2b : High magnification of part of Fig 2a. The surface of the lymph capillaries is smooth and possesses many pores (about 0.1 - 2 μm, arrows) which are observed mainly between endothelial cells. There are also small pores which gather together and appear like a sieve in the endothelial cells (white arrows). Fibers corresponding to anchoring filaments are seen (arrowheads).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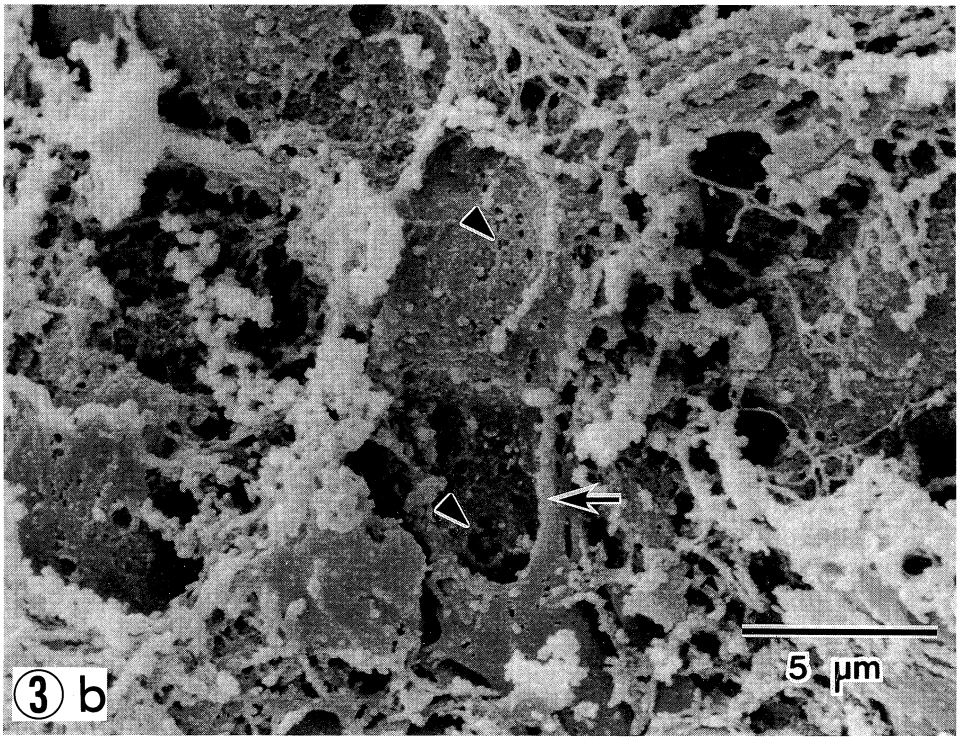
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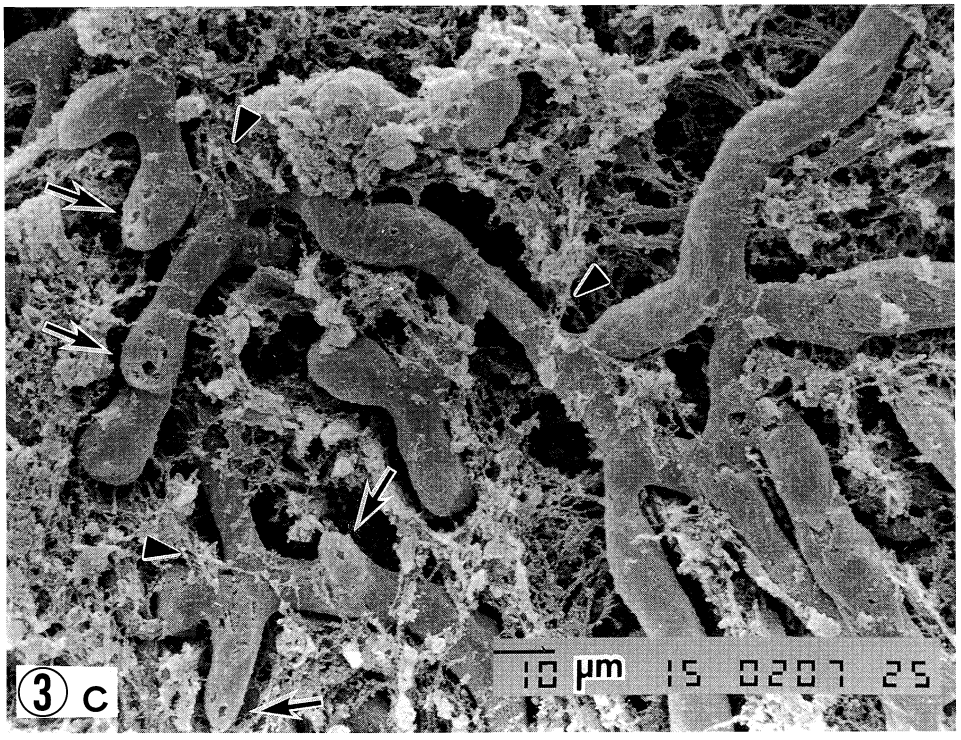
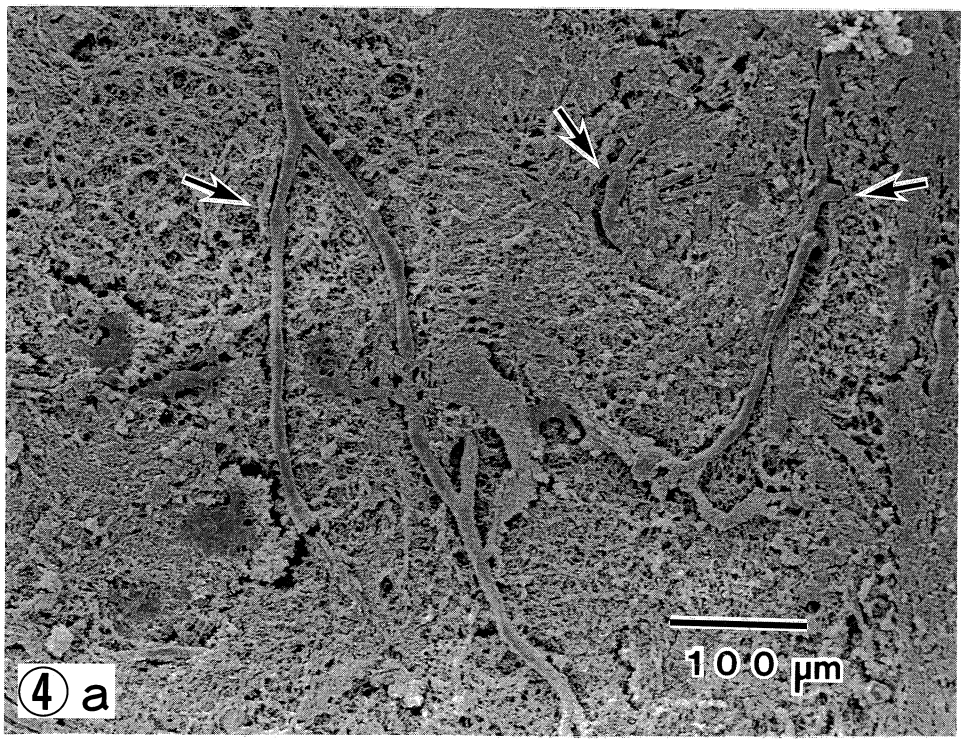


Fig 3. Type-2 lymphatic capillaries.

3a : SEM after stripping of the liver capsule at a deep layer, followed by chemical digestion. The Type-2 lymphatic capillaries exist above Type-1 lymphatic capillaries. The diameters range between 5 and 10 μm, and they run in all directions, anastomosing and crossing one another. They have many blind-ended branches (arrows). No pericytes are seen.

3b : Fracturing of one of the lymphatic capillaries. The wall consists of only a single endothelial cell layer (arrow), and pores are seen (arrowheads).

3c : High magnification of the lymphatic capillaries seen in Fig 3a. The surface is smooth and has pores (about 0.1-2 μm) existing in interendothelial areas, especially in the blind-ended branches (arrows). Fibers corresponding to anchoring filaments are seen (arrowheads).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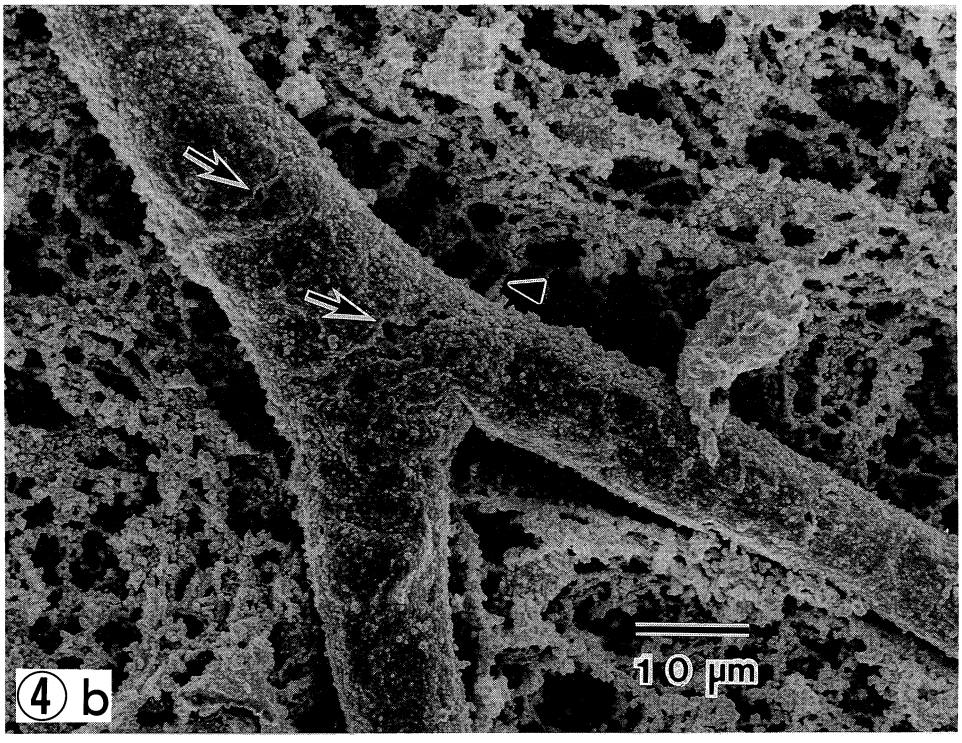
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DISCUSSION

In the liver, lymph is generated in the space of Disse and interior and superficial systems are known as lymph outflow pathways.[17] In the interior system, the lymphatic capillaries in the portal tract form a complex plexiform arrangement. These portal lymphatic vessels converge at the porta hepatis and drain into the lymph nodes of the hilus. Some other lymphatics leave the liver through surrounding hepatic veins. In the superficial system, the lymph capillary network in the hepatic capsule joins thicker lymph vessels which leave the liver.[15]

The morphology and architecture of the hepatic lymph capillaries; i.e., the initial inflow pathway of the abundant hepatic lymph, have been investigated by TEM[7-9] and stereomicroscopy using the injection method.[15] The microstructural morphology of the endothelial cells can be studied by TEM, but the three-dimensional architecture of the lymph capillaries cannot. The three-dimensional arrangements of the intrahepatic lymph capillaries in the rabbit liver have been demonstrated by SEM using corrosion casts.[10] In that study, the casts were prepared by injecting resin into the common bile duct and allowing it to leak from the small bile duct and drain into the lymphatics. It is unclear whether the initial lymphatics near the hepatic parenchyma were cast or not. Furthermore, this method does not permit observation of the external surfaces. The stereoscopic fine architecture of the initial lymphatics of the human liver have not yet been thoroughly observed.

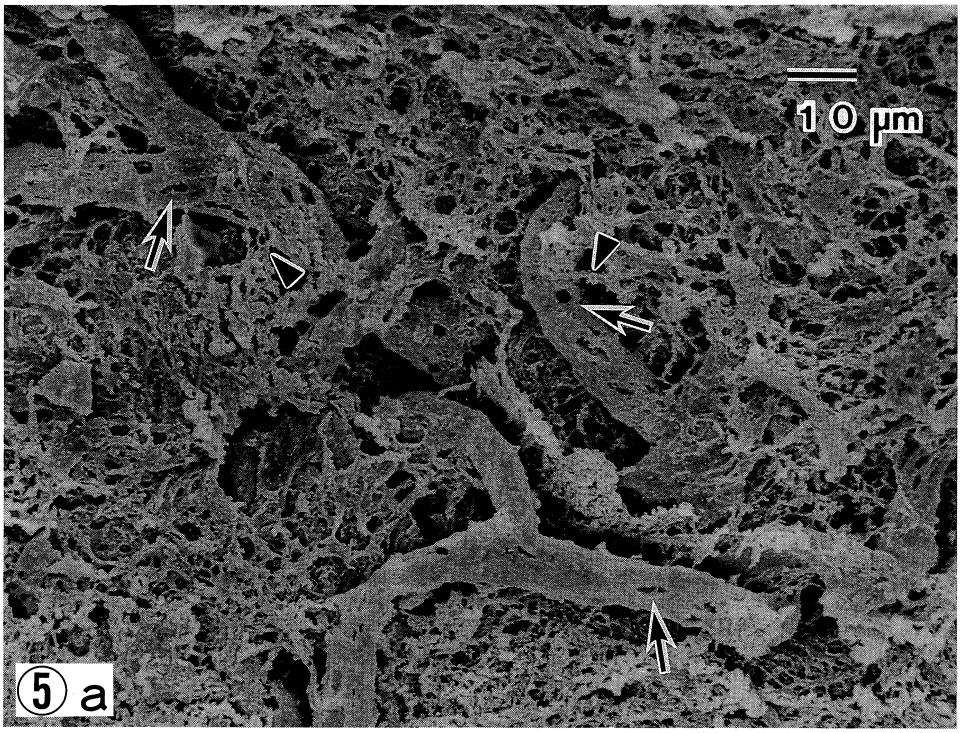
The capsular lymphatics of the human liver are present in the subcapsular connective tissue, and the lymph capillaries form a very fine mesh in the connictive tissue.[15] Tokumitsu S carried out a SEM three-dimensional study of the hepatic lymph capillaries from the external surface, which was exposed by the chemical digestion method following manual stripping of the hepatic capsule.[11] However, the morphology of the initial lymphatics was not clarified. Therefore, the author extended Tokumitsu's study and observed the hepatic subcapsular lymph capillary network in detail.

The lymph capillaries are morphologically characterized by uneven diameters, deficiency of pericytes, the presence of blind-ended branches and anchoring filaments, interendothelial openings as the site of lymph absorption, frequent deficiency of the basement membrane, and the absence of small stoma in endothelial cells.[18] The present observation of the hepatic subcapsular lymph capillaries also revealed an uneven diameter, lack of pericytes, the presence of blind-ended branches, and anchoring filaments. Most of the pores of the lymph capillaries observed by the author in the present study were considered to be interendothelial openings because of their arrangement in the endothelial cells' lines; i.e., interendothelial, especially in a tortoise shell pattern.

←Fig 4. Type-3 lympaphtic capillaries.

4a: SEM after stripping of the liver capsule at a deep layer, followed by chemical digestion. Type-3 lymphatic capillaries existing above Type-2 lymphatic capillaries are shown (arrows). Their diameter, between 10 and 15 μm. is wider than the latter, and they run relatively straight and long.

4b: High magnification of the lymphatic capillaries seen in Fig 4a. The surface is smooth, and has a few pores in interendothelial areas (arrows). No pericytes are seen. Few anchoring filaments are seen (arrowhead).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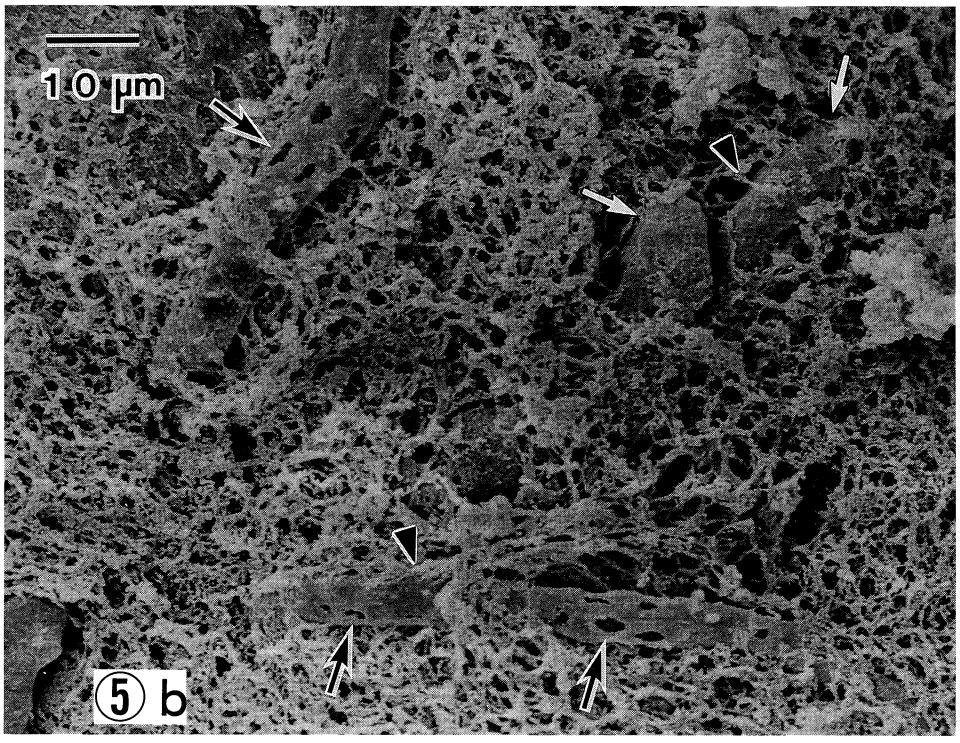
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Mödis L and Martinez-Hernandez A[19] reported that hepatocytes modulate the hepatic microvascular phenotype; i.e., the sinusoidal phenotype with fenestrations lacking diaphragms, and they postulated that this modulation is exerted either by secreted soluble cytokines or the extracellular matrix. Therefore, the author speculated that hepatocytes may also modulate the phenotype of the hepatic lymph capillaries existing just over the parenchyma. It was assumed that the pores appearing like a sieve in the endothelial cells of the Type-1 lymphatic capillaries (Fig 2b, white arrows), except for the interendothelial openings, are peculiar to the lymphatic capillaries of the liver.

The author divided the hepatic subcapsular lymphatic capillaries into the following three types: Type-1, lymphatic capillaries with many small pores, which spread in a net-like pattern just above the hepatic parenchyma (Fig 2); Type-2, lymphatic capillaries with many blind-ended branches and small pores, particularly in the blind-ended areas (Fig 3); Type-3, lymphatic capillaries with only a few small pores, which ran in relatively straight and long patterns (Fig 4).

The type-1 lymphatic capillaries of the liver capsule had an uneven diameter between about 5-20 μm and dilated partially like a cyst (Fig 2). They showed a close net-like distribution in the deepest layer of the subcapsular connective tissue; namely, just above the parenchyma. The interface between overlapping endothelial cells of lymphatic capillaries; i.e., the interendothelial openings, can easily open inward. As a result, lymph can easily enter the lymph capillaries. Once lymph has entered the lymph capillaries, its reflux to the stroma is prevented by the valvular structure of the interendothelial openings.[20] Hepatic lymph has two characteristics because of its origin in Disse space. One is its large quantity, and the other is its high protein content approximately corresponding to that in the plasma.[1,2] The author believes that the Type-1 lymphatic capillaries with many small pores spreading like a network just above the hepatic parenchyma could be helpful for collecting and drainage of the large amount of protein rich lymph from the Disse space. These lymphatic capillaries, existing just above the parenchyma, could absorb the lymph from the Disse space like a sponge and transmit it. The Type-1 lymphatic capillaries are considered to be initial lymphatics of the hepatic capsule and specific to the liver.

The Type-2 lymphatic capillaries, with many blind-ended branches and with small pores particularly in the blind-ended areas, ran in all directions, showing a net-like structure (Fig 3). Their diameter was about 5-10 μm. They were located over the initial lymphatics (Type-1 lymphatic capillaries). The morphology of these lymphatics was consistent with that of the lymphatic capillaries of other organs and tissues already mentioned.[18] It was speculated that both the quantity and protein density of the hepatic lymph may markedly fall as it moves away from the parenchyma after absorption by Type-1

←Fig 5. Subcapsular lymphatic capillaries of Budd-Chiari syndrome.

5a: SEM after stripping of the liver capsule followed by chemical digestion. Lymphatic capillaries anastomose and cross one another. Their diameter is about 5-10 μm. The surface is smooth, and has many pores (about 0.1-3 μm, arrows) between endothelial cells. Fibers corresponding to anchoring filaments are seen (arrowheads). No pericytes are seen.

5b: Some of the lymphatic capillaries are abruptly blind-ended (white arrows). pores: arrows. anchoring filaments: arrowheads.

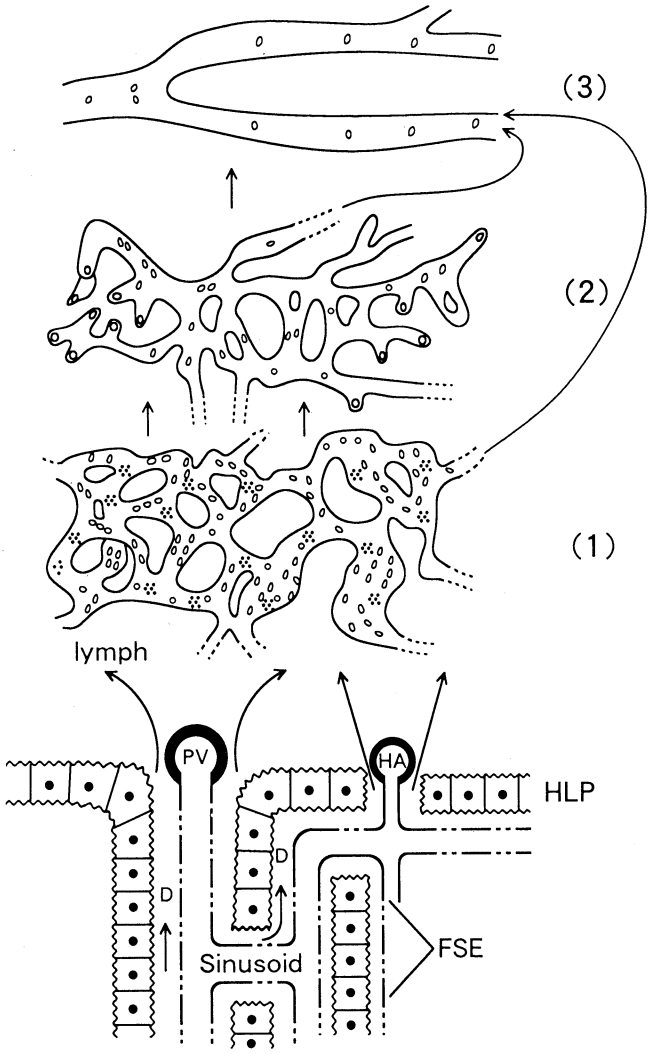

Fig 6. Schematic diagram of hepatic lymph flow and subcapsular lymphatic capillaries in the normal liver.

(1) Type-1, initial lymphatics with many small pores, spreading mesh-like just above the hepatic parenchyma.
(2) Type-2, lymphatic capillaries with many blind-ended porous branches, running stereoscopically in all directions.
(3) Type-3, aggregate vessels of lymphatic capillaries showing a relatively straight and long running course.

The arrows indicate the lymph movement towards the lymphatic capillaries and the pathway for the lymph.
PV: subcapsular portal vein. HA: subcapsular hepatic artery. HLP: hepatic limiting plate. FSE: fenestrated sinusoidal endothelium. D: space of Disse.

lymphatic capillaries, and that Type-2 lymphatic capillaries may mainly collect the lymph from the blood capillaries in the capsular connective tissue. The author considered this to be the reason why the Type-2 lymphatic capillaries are similar to lymph capillaries in other organs and tissues.

The type-3 lymphatic capillaries, which ran in relatively straight and lengthy patterns and which had only a few small pores (Fig 4), were considered to be drainage lymph capillaries from their morphological characteristics.

Kitazume N carried out a detailed observation of superficial lymphatic capillaries of the human liver under a stereoscopic microscope, using the injection method.[15] According to his report, the diameter of the superficial lymphatic capillaries of the liver ranges from 10 to 15 μm. The capillaries form a network of from tens to over hundreds of loops per surface side of an individual liver lobule, and they look like a sheet within the subcapsular connective tissue adjoining the hepatic parenchyma. In their diameters and running network patterns, these superficial lymphatic capillaries resemble the Type-2 lymphatic capillaries. Discrepancies between the morphological features of Kitazume's and the author's studies may be due to the use of different methods.

The author's findings are shown in the schema (Fig 6).

In the liver of Budd-Chiari syndrome, the hepatic lymph protein level is decreased because of sinusoidal capillarization and fibrosis of the Disse space as in liver cirrhosis, while the quantity of lymph is increased.[13] In Budd-Chiari syndrome, Type-1 lymphatic capillaries, which were seen in the normal liver, were not observed. The author assumed that they collapsed and disappeared in the widespread fibrosis following centrilobular fibrosis and because of accentuaded periportal regeneration resulting in nodule formation in the chronic course of Budd-Chiari syndrome. The subcapsular hepatic lymph capillaries of this syndrome showed fine structures similar to Type-2 in normal liver except for enlargement of the pores that were interendothelial openings. These findings were also believed to explain the pathophysiology of this syndrome; that is, an increase in the quantity of lymph absorbed but a decrease in protein density.

In liver cirrhosis, Tokumitsu S reported that, the subcapsular lymphatic capillaries have the morphological characteristics of lymphatic capillaries in general organs and tissues excluding the liver. The reason for this seems to be that the protein level of the lymph is decreased by changes in sinusoidal endothelial cells; i.e., capillarization and fibrosis of the Disse space in liver cirrhosis. In other words, the quality of the lymph in patients with liver cirrhosis becomes similar to that of other organs and tissues, and it becomes unnecessary to absorb lymph with a high protein concentration similar to the plasma protein concentration as in the normal liver.[21]

The ultramicrostructures of the hepatic lymph capillaries revealed by SEM after manual stripping of the liver capsule followed by the chemical digestion method were well adapted to the biophysical characteristics of the hepatic lymph both in health and disease.

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