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Sclerosed Hemangioma Accompanied by Multiple Cavernous Hemangiomas of the Liver

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: **Male, 81**
Final Diagnosis: **Sclerosed hemangioma**
Symptoms: —
Medication: —
Clinical Procedure: **Autopsy**
Specialty: **Diagnostics, Laboratory**

Objective: **Rare disease**

Background: A sclerosed hemangioma of the liver, an extremely rare type of benign hepatic tumor, was found at autopsy.

Case Report: An 81-year-old Japanese man was admitted to our hospital for surgical resection of squamous cell carcinoma of the skin in his left forearm. At admission, serological tests for hepatitis B surface antigen and hepatitis C antibody were negative with no evidence of cirrhosis. At 2, 3, and 5 months after the removal of the forearm tumor, skin grafting was performed because of unhealed skin ulceration. Although anti-bacterial drugs were prescribed, the patient died after the 3rd skin graft (5 months after the surgery) because of pneumonia. During the treatment course, the patient was diagnosed as having multiple liver masses suspected to be cysts of the liver based on non-contrasted computed tomography results. Autopsy revealed a sclerosed hemangioma occupying the entire left lobe accompanied by multiple small cavernous hemangiomas in the right lobe of the liver.

Conclusions: Sclerosed hemangioma, a rare benign disease, occurred in association with degeneration and sclerosis of cavernous hemangiomas of the liver. The VEGF pathway may be involved in the genesis of cavernous and sclerosed hemangioma of the liver.

MeSH Keywords: **Hemangioma • Hemangioma, Cavernous • Immunohistochemistry • Liver • Vascular Endothelial Growth Factor • Vascular Endothelial Growth Factor Receptor**

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/893934>



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Background

In 1983, sclerosed hemangioma, an unusual hemangioma of the liver, was first described by Shepherd and Lee by the term “solitary necrotic nodule” [1]. Solitary necrotic nodule is a broad term that includes not only sclerosed hemangiomas but also parasitic infection and trauma [2]. Sclerosed hemangioma is characterized by sclerosis and hyalinization occurring in association with degeneration of a cavernous hemangioma of the liver [3]. Although sclerosed hemangioma is a benign condition, its radiological features resemble those of hepatic malignancies such as hypovascular adenocarcinomas including cholangiocarcinomas, fibrolamellar hepatocellular carcinomas, or metastatic liver cancers [4]. We herein report a case of sclerosed hemangioma accompanied by cavernous hemangiomas of the liver and discuss the probable pathogenesis of the disease.

Case Report

An 81-year-old Japanese man was admitted to our hospital for surgical resection of squamous cell carcinoma of the skin in his left forearm. At admission, the hematologic and blood chemistry data were as follows: red blood cell count, 3.28 million cells/ μ L; hemoglobin, 9.1 g/dL; white blood cell count, 9 700/ μ L; platelet count, 298 000 / μ L; blood urea nitrogen, 29 mg/dL; creatinine, 0.77 mg/dL; aspartate aminotransferase, 18 IU/L; alanine aminotransferase, 31 IU/L; and c-reactive protein (CRP), 0.529 mg/L. Serological tests for hepatitis B surface antigen (HBs-Ag) and hepatitis C antibody (anti-HCV) were negative. Before the skin tumor removal, carcinoembryonic antigen (CEA) was within normal levels, but squamous cell carcinoma antigen (SCC-Ag) remained high after the surgery. The

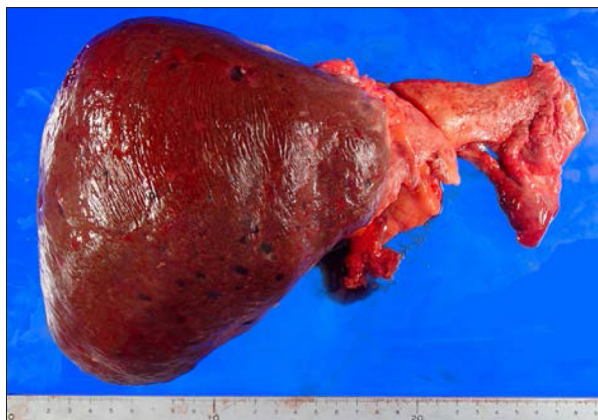


Figure 1. Macroscopic appearance of the surface of the liver. The left lobe is completely occupied by a solid grey-white mass, which indicates a sclerosed hemangioma. Small red nodules sporadically seen in the right lobe indicate cavernous hemangiomas.

patient's physical examination was unremarkable. At 2, 3, and 5 months after the removal of the forearm tumor, skin grafting was performed due to unhealed skin ulceration. Although anti-bacterial drugs were prescribed, the patient died of pneumonia after the 3rd skin graft. During non-contrasted computed tomography (CT) performed in the preoperative workup, the patient was incidentally diagnosed as having multiple liver nodules less than 1 cm in size that were suspected to be cysts. The patient did not report any abdominal symptoms.

Case Report

Macroscopically, the left liver lobe was completely replaced by a firm gray-white mass measuring 10×7×3 cm, and multiple <1-cm red sponge-like nodules were scattered on the right lobe (Figure 1). The red sponge-like nodules were detected by non-contrasted CT as cysts, but the sclerosed mass located in the left lobe was not detected when the patient was alive. Microscopically, the grayish white mass exhibited narrow and irregular vessels that were embedded in thickened sclerotic and hyalinized collagenous tissue. Within the thick collagenous stroma, normal-looking hepatic cell cords and bile ducts focally remained (Figure 2A). Narrow and irregular vessels were lined by flattened endothelial cells without cytological atypia or mitotic activity (Figure 2B) and few erythrocytes were seen within the lumen. The stroma contained numerous elastic fibers seen by elastic van Gieson staining (data not shown). Immunohistochemistry was performed by using EnVision™+ Single Reagents (Dako, Glostrup, Denmark). In the sclerosed area, endothelial cells were positive for CD31 (Acris Antibodies, Herford, Germany) and CD34 (Abcam, Cambridge, UK; Figure 3A) and negative for D2-40 (Nichirei Biosciences, Tokyo, Japan). In addition, vascular smooth muscle cells and fibroblasts or myofibroblasts surrounding endothelial cells that were embedded in the stroma were positive for α -smooth muscle actin (Dako; Figure 3B). Furthermore, vascular endothelial growth factor (VEGF, Santa Cruz Biotechnology, Santa Cruz, CA, USA; Figure 3C) and its receptors, VEGFR1 (Santa Cruz Biotechnology, data not shown) and VEGFR2 (Cell Signaling Technology, Danvers, MA, USA; Figure 3D), were positive in fibroblasts or myofibroblasts as well as in endothelial cells. However, estrogen receptor and progesterone receptor were invariably negative (data not shown). Based on these results, the lesion was diagnosed as sclerosed hemangioma. In contrast to the sclerosed area, the red sponge-like nodules scattered within non-cirrhotic liver were diagnosed as cavernous hemangiomas; multiple vascular spaces of various sizes were lined by a single layer of flattened endothelial cells (Figure 4). In these areas, immunohistochemistry showed similar results to the sclerosed lesion.

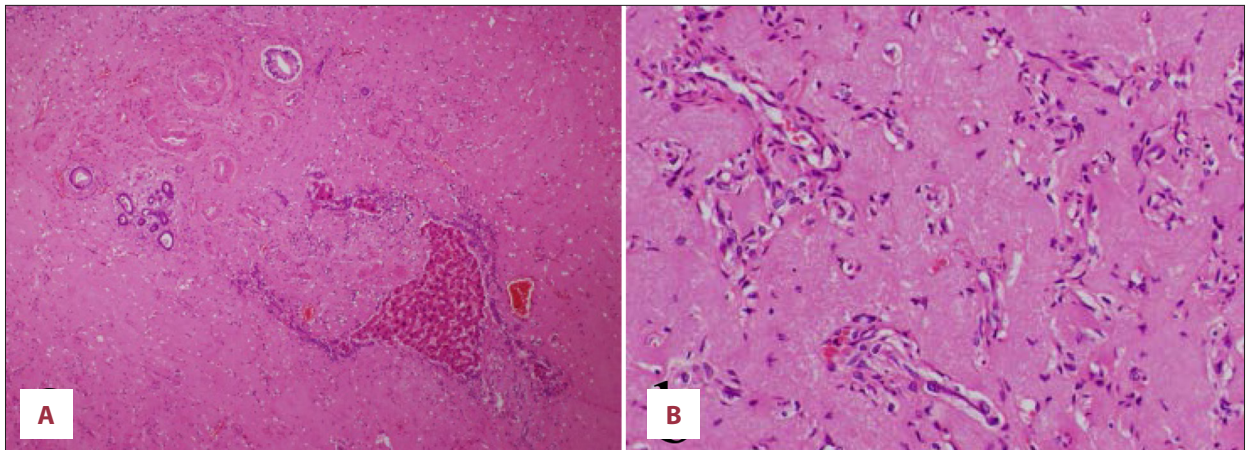


Figure 2. Microscopic features of sclerosed hemangioma. (A) Within the thick collagenous stroma, normal-looking hepatic cell cords and bile ducts are focally remaining (hematoxylin and eosin staining; HE $\times 40$). (B) Narrow and irregular vessels without cytological atypia or mitotic activity are embedded within the stroma (HE $\times 200$).

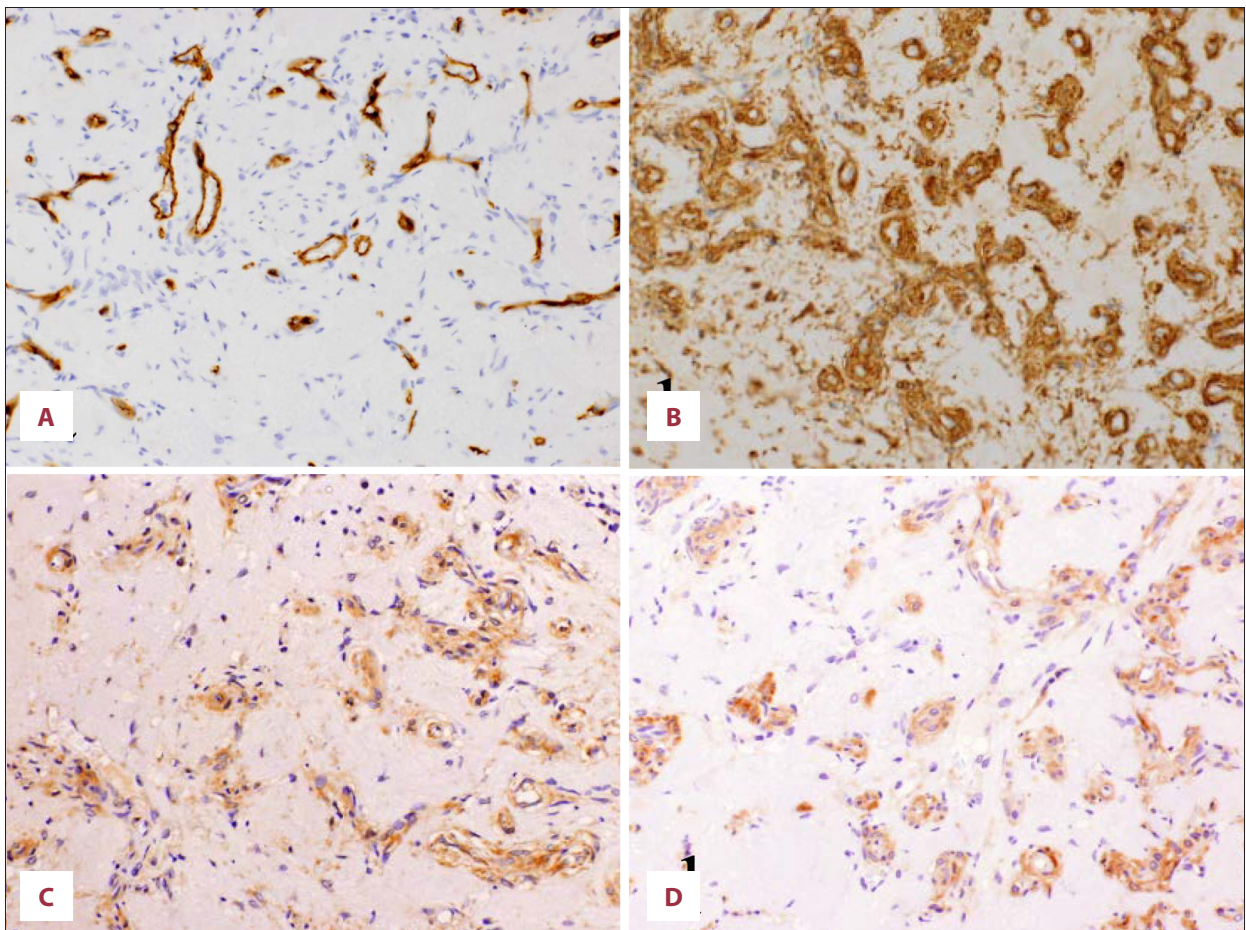


Figure 3. Immunohistochemistry of sclerosed hemangioma. (A) Vessels are clearly labeled with CD34 (CD34 $\times 200$). (B) Vascular smooth muscle cells, fibroblasts, or myofibroblasts are α -smooth muscle actin-positive (α -smooth muscle actin $\times 200$). (C) Endothelial cells, fibroblasts, or myofibroblasts are VEGF-positive (VEGF $\times 200$). (D) Endothelial cells, fibroblasts, or myofibroblasts are also VEGFR2-positive (VEGFR2 $\times 200$).

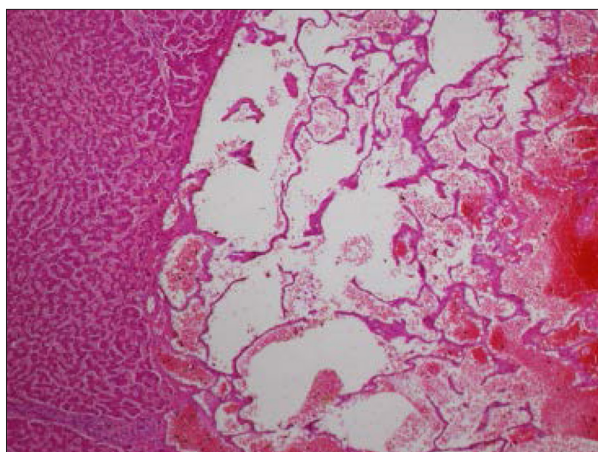


Figure 4. Microscopic features of cavernous hemangioma (HE ×40).

Discussion

Cavernous hemangioma is the most common benign tumor of the liver [5] with a frequency of 0.4% to 20% in autopsy studies [6]. In contrast, sclerosed hemangioma is a rare condition found in only 2 of 1000 autopsy cases [7]. Sclerosed hemangioma accompanies cavernous hemangioma or preexisting cavernous hemangioma changes to sclerosed hemangioma over a period of many years [3]; sclerosed hemangioma is thought to be the terminal stage of degeneration of a cavernous hemangioma. Cavernous hemangioma is more commonly seen in young adult women while sclerosed hemangioma is seen more in older women [4]. The frequency of cavernous hemangioma acquiring sclerosis does not seem to be high, and the lesion formation requires many years. We have reviewed the English literature from PubMed Central and collected precisely described case reports that included pathological information. Eight cases including the present case were collected

under the keyword “sclerosed hemangioma” and are listed in Table 1 [3,4,8–12]. The patients had a relatively high age (range, 40–81; average, 66.3 years) and male: female ratio was 1:1. Characteristically, in the present case, both sclerosed hemangioma and multiple cavernous hemangiomas were synchronously found in the liver at autopsy, and asynchronous occurrence was reported in another 1 case [3].

Sclerosed hemangioma can pose a diagnostic challenge; it contains areas of degeneration secondary to thrombosis, necrosis, and calcification that make precise radiological diagnosis very difficult [13,14]. Sclerosed hemangioma is frequently misdiagnosed as intrahepatic malignancy or metastatic lesions, for which a hepatectomy is performed. In 7 of 8 reported cases of sclerosed hemangioma from the literature, malignancy could not be excluded (Table 1). In the present case, as contrasted CT was not performed, non-contrast CT captured multiple cavernous hemangiomas misdiagnosed as cysts of the liver and the sclerosed hemangioma could not be detected.

Cavernous hemangioma undergoes degeneration and collagenous replacement that creates sclerosed hemangioma [3]. Thrombi in various stages of organization with areas of infarction may lead to sclerosed hemangioma [15]. In sclerosed hemangiomas, most vessels are occluded. Molecules or molecular pathways involved in the occurrence of hemangioma and the development of sclerosed hemangioma have been speculated. One report states that mast cells may secrete down-regulators of angiogenesis and play a role in hepatic fibrosis, which may participate in the occurrence of sclerosed hemangioma [16]. Another report describes the role of estrogen in the growth and development of liver hemangiomas [17]; estrogen enhances whereas tamoxifen retards the development of liver hemangioma in the mouse system [18]. However, the present male patient showed no evidence of hyperestrogen

Table 1. Reported cases of sclerosed hemangioma of the liver.

| Case | Age | Sex | Location | Size (mm) | CH | Imaging | Reference |
|------|-----|-----|----------|-----------|----|-------------|--------------|
| 1 | 40 | M | L-lobe | 40 | – | HCC | 8 |
| 2 | 67 | F | Med-seg | 40×30 | – | METAST (GC) | 9 |
| 3 | 77 | F | S5/6 | 100 | – | CCC, FLC | 4 |
| 4 | 52 | M | S6 | 21×16 | – | SH/HCC | 10 |
| 5 | 75 | F | R-lobe | 30 | – | CCC, METAST | 11 |
| 6 | 75 | M | S8 | 80×70 | – | METAST (GC) | 12 |
| 7 | 63 | M | S8 | 11×11×10 | + | SH/HCC, CCC | 3 |
| 8 | 81 | M | L-lobe | 100×70×30 | + | ND | Present case |

CCC – cholangiocarcinoma; CH – cavernous hemangioma; FLC – fibrolamellar hepatocellular carcinoma; GC – gastric carcinoma; HCC – hepatocellular carcinoma; METAST – metastasis; ND – not detected; SH – sclerosed hemangioma.

status in his history, and estrogen and progesterone receptor were both negative in the cavernous and sclerosed hemangioma lesions. Estrogen cannot explain the occurrence of hemangioma and the development of sclerosed hemangioma in the present case. In contrast, VEGF, VEGFR1, and VEGFR2 were positive not only in endothelial cells but also in fibroblasts or myofibroblasts surrounding endothelial cells and within the sclerosed stroma. Transgenic rabbits with increased VEGF expression develop hemangiomas in the liver [19], and size of liver hemangioma regress following blockage of VEGF pathway [20]. Therefore, the VEGF pathway in both autocrine and paracrine fashion may partially explain the occurrence and

development of this rare tumor. However, the precise cause of the sclerosing process and whether this process is initiated by the endothelial cells or by the surrounding fibroblasts needs further study.

Conclusions

The VEGF pathway may be involved in the etiology and pathogenesis of cavernous and sclerosed hemangioma, a rare benign disease of the liver. Sclerosed hemangioma should be taken into consideration during the differential diagnosis of liver tumors.

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