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INVASIVE CHARACTER OF MALIGNANT ENDOTHELIAL CELLS IN VINYL-CHLORIDE-INDUCED LIVER ANGIOSARCOMA

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ABSTRACT

Two cases of vinyl-chloride-induced angiosarcoma of the liver were investigated with special reference to the invasive character of malignant endothelial cells. Histological findings of the liver were similar in both cases. The liver angiosarcoma was multicentric and consisted of three portions: a peripheral parenchymal area, an intermediate mottled area, and a central cavernous area. Microscopically the intermediate area showed a mixture of fibrosis and cell infiltration of various patterns. At the periphery, yellowish brown parenchymal tissues remained and were always associated with sinusoidal changes, from non-cellular dilatation to trabecular growth of the small round cells. Under electron microscope, the small round cells showed direct contact with red blood cells and hepatocytes. Thus, the sinusoidal small cell infiltration is thougth to be an initial lesion of angiosarcomatous transformation. Because none of the liver is free from these sinusoidal changes, partial hepatectomy would not be indicated even in a patient with few cavernous lesions.

Key Words: Vinyl chloride, Angiosarcoma, Cavernous tissue, Liver tumor, Endothelial cells.

INTRODUCTION

Vinyl-chloride-induced liver angiosarcoma is still a serious problem in industrial medicine because of the long time-lag between exposure and development, and because of its poor prognosis.[1)] In 1974 and 1985 two patients with the disease were found in the Nagoya industrial region and have been reported about in detail previously.[2,3)] New diagnostic techniques introduced during the last decade provide a reliable image of the liver structures but have not changed the prognosis of the disease. The current study focuses on the structural characteristics of the malignant endothelial cells, which determine the poor prognosis.

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PATIENTS AND METHODS

The first patient[2] was found in 1974, the second in 1985[3] (Table 1). Both patients had a long history of inhalation of vinyl chloride monomer and died within fifteen months and four months after detection of the disease, respectively. Liver specimens obtained at autopsy were either formalin-fixed, paraffin-embedded, and stained histochemically for light microscopy, or osmium-fixed and epoxy resin-embedded for electron microscopy. Ultrathin sections were observed under a JOEL 100C electron microscope.

RESULTS

The structure of the liver with angiosarcoma was similar in both patients though its size was quite different. Macroscopically, the hepatic angiosarcoma was multicentric and consisted of three portions: a peripheral parenchymal area, an intermediate mottled area, and a central cavernous area. Two thirds of the liver was replaced by cavernous tumors which were partially hemorrhagic and necrotic. The blood-filled, cavernous spaces were irregular in shape and varied from 1 mm up to 3 cm in diameter. Microscopically, spindle-shaped tumor cells exhibited both papillary and cavernous growth patterns. The hepatic cords had completely disappeared and the wall of the cavernous vascular spaces was irregularly thickened by fibrous connective tissue.

The intermediate mottled areas consisted of mixed tissue of fibrosis and cell infiltration of various sizes and forms. These hyperchromatic tumor cells showed a wide variation in arrangement: papillary, trabecular and anaplastic. In general, infiltration was sinusoidal, but in some areas capillary or anaplastic tumor cells showed nodular growth. Again, there were a number of cavernous, hemorrhagic and necrotic foci, though they were small in size compared with the central cavernous area.

At the periphery, yellowish brown parenchymal tissues remained and were always associated with sinusoidal change and fibrosis (Fig. 1). A variety of sinusoidal lesions ranged from non-cellular dilatation to nodular growth of small round cells with hyperchromatic nuclei. Occasionally, the small round cells infiltrated to line the sinuses instead of slender endothelial cells (Fig. 2). In addition, the small round cells, either in clusters or diffusely scattered, infiltrated the mottled area around the cavernous tissue.

Under electron microscope, the small round cells were poor in cytoplasmic organelles (Fig. 3). Frequently red blood cells appeared in the central cavity of the cells, suggesting endothelial origin. In some areas the small cells were interlinked directly with hepatocytes. Thus, angiosarcomatous transformation was seen in a wide area from the peri-cavernous zone to the peripheral parenchymal tissue.

DISCUSSION

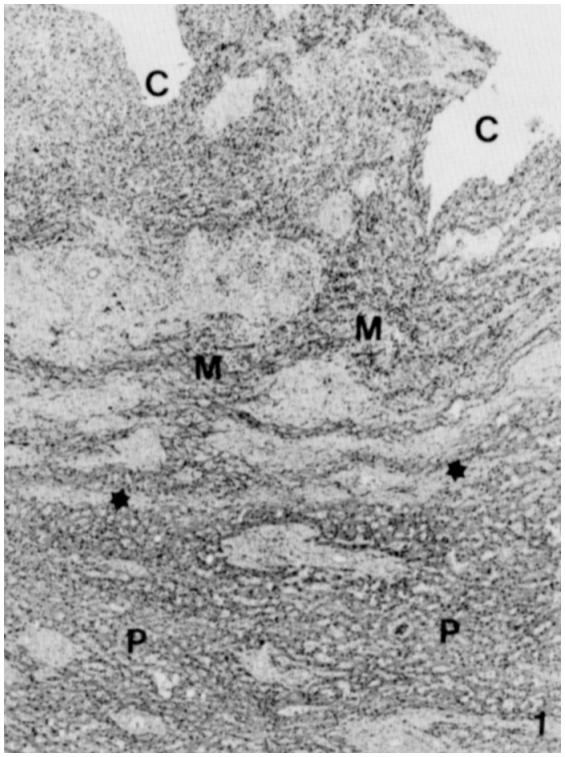
Fortunately, this malignancy is rare in Japan despite her large vinyl chloride production when compared with other industrial countries. Until 1988, only three cases of this industrial malignancy had been reported in Japan.[4] Two of them were found in the Nagoya industrial district and were treated by us. During the last decade, liver imaging had progressed enough that we could detect peri-cavernous lesions as well as cavernous tissues in the second patient. His prognosis, however, was as poor as that for the first patient, who had been found and treated 10 years earlier. New imaging systems including ultrasonography and computed tomography did not result in an improved prognosis for the patient with this malignant liver disease.

Because the above two cases have been reported earlier, the present paper focuses on the invasive character of the malignant tumor, which may be a major factor in determining the prognosis of the disease. The liver lesions of our patients with vinyl-chloride-induced liver angiosarcoma were characterized by multicentric, cavernous blood clusters surrounded by a mixed lesion of malignant cell infiltration and subcellular fibrosis like that described by Thomas and Popper.[5] In addition, we confirmed another histological aspect of the disease, namely, that it is hard to determine the border of malignancy because of indefinite invasion of malignant cells. In fact, there were residues of parenchymal tissues in the periphery of the liver. Most hepatocyte cell plates, however, were found to be lined directly by small round cells with hyperchromatic nuclei. Under electron microscope, the small cells, characterized by their poor organelles, had direct interaction with the hepatocellular membrane. Spatial relation of these malignant cells to the vasculature was also noted; the small round cells infiltrated to line the sinuses filled with red cells instead of slender endothelial cells. Based on these observations, we postulate that the small round cells play an important role in angiosarcomatous transformation, and the sinusoidal change infiltrated with these cells is an initial lesion of vinyl-chloride-induced angiosarcoma of the liver. This change was so diffuse that none of the liver was entirely free of angiosarcoma at the time of autopsy.

The diffuse infiltration of malignant endothelial cells is not only a histological characteristic of this liver disease, but it is also another important implication for the treatment of patients. Because of the difficult demarcation of malignant lesions, partial hepatectomy is not indicated even in a patient with little cavernous tissue. Liver transplantation, which is not performed in Japan because of ethical dispute, would probably be the treatment of choice.

Table 1. Clinical Features of Patients

	Case 1	Case 2
Age	53	55
Sex	male	male
Entry	7/1974	5/1985
Outcome	death in 15 M	death in 4 M
Exposure	3/1953–7/1974	7/1965–5/1979
Liver Weight	2300 g	6300 g
Macroscopic findings	liver angiosarcoma metastasis: lung Douglas' cul-de-sac bloody ascites splenomegaly: 390 g	liver angiosarcoma no metastasis bloody ascites splenomegaly: 210 g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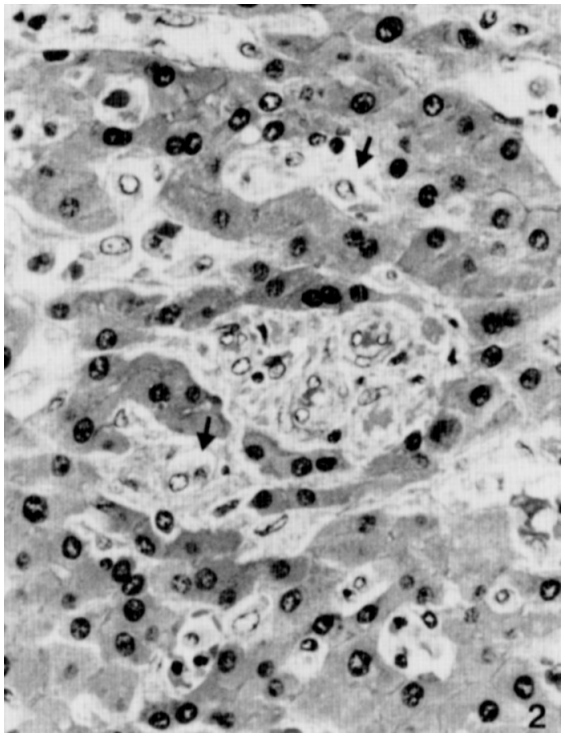
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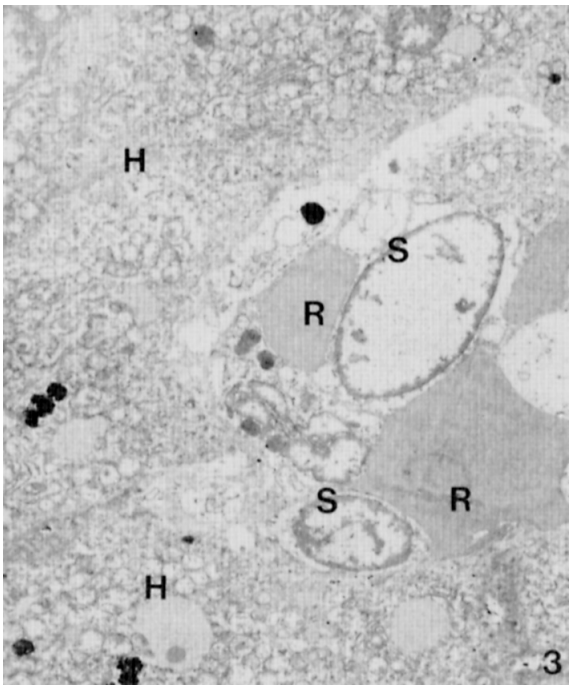

Fig. 1. The peripheral parenchymal tissues of liver angiosarcoma. In addition to parenchymal cell cords (P), there are intermediated mixed lesions of infiltration and fibrosis (M), and cavernous tissues (C). Note subendothelial fibrosis (stellulae). Haematoxylin-eosin, × 36.

Fig. 2. Sinusoidal dilatation with small round cell infiltration (arrows) among parenchymal cells. This lesion looks normal macroscopically. Haematoxylin-eosin, × 330.

Fig. 3. Ultrastructures of the small round cells (S) are characterized by their poor cytoplasmic organelles and their spatial relation to red blood cells (R) and hepatocytes (H). Stained with uranyl acetate and lead citrate, × 3,300.

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