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A Clinicopathologic Study of Infantile Hemangioendothelioma of the Liver

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=Abstract=**Infantile hemangioendothelioma which is the most common primary vascular neoplasm of the liver in infancy and early childhood, frequently poses diagnostic problems due to its characteristics, and thus the authors performed a retrospective clinicopathological analysis of 5 cases of infantile hemangioendothelioma of the liver. All the cases were found before 6 months of age, and there were two females and three males. An abdominal mass and jaundice comprised main symptoms, and associated cutaneous hemangiomas were not present. A case had features of Kasabach-Merritt syndrome. The tumors were well circumscribed, solid masses with areas of necrosis and hemorrhage, and microscopically were composed of numerous vascular channels of varying size, separated by fibrous stroma containing a single layer of flat or plump endothelial cells which were located on the luminal side of the vascular reticulin sheath. Immunohistochemical staining demonstrated factor VIII-related antigen in the tumor cells, and ultrastructurally, relatively well formed vascular lumina were surrounded by sparsely arranged elongated spindle cells having parallel processes. Among the divergent primary hepatic neoplasms in infancy and childhood, this tumor was found to have rather distinct clinicopathological features, and the detailed differential points from other types of neoplasm were discussed along with its anticipated biologic behaviour.**

Key Words: *Hemangioendothelioma, Liver, Infant, Neoplasm*

INTRODUCTION

Infantile hemangioendothelioma of the liver is a benign vascular tumor of infancy and early childhood, and it is extremely rare when compared with its counterparts of the skin and soft tissue(Dehner and Ishak 1971). Because it is found as a solitary or multiple parenchymal lesion of the liver, it is of the utmost importance to differentiate this lesion from other kinds of primary hepatic neoplasm because the pathological spectrum of hepatic neoplasm in this period is rather divergent.

In the present study, we performed an analysis of the clinicopathological aspects of infantile hemangioendothelioma of the liver to document its significance in infancy and early childhood.

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MATERIALS AND METHODS

From the files of the Department of Pathology of Seoul National University Children's Hospital, 5 cases of infantile hemangioendothelioma of the liver during a period from 1985 to 1991, among which one was previously described by Suh *et al*(1987), were found and their clinicopathological findings were analyzed. Four cases were surgically resected and one was an autopsy case. In each case, 5 to 15 histologic sections were reviewed microscopically, and for the detection of expression of factor VIII-related antigen, immunohistochemical staining was performed using the avidin-biotin complex method. In three cases, fresh tumor tissues were sampled and fixed in glutaraldehyde, and sequentially processed for electron microscopic examination.

RESULTS

Clinical Features

Among the 5 cases, there were 2 males and 3 females, and the age distribution was from 8 days to 6 months. An abdominal mass was the main presenting symptom in all cases and 3 cases otherwise had no significant symptoms. On physical examination, the masses were nontender and rubbery firm.

A one month-old male baby had icteric sclera, periorbital jaundice since 2 days after birth, peripheral cyanosis, and hepatosplenomegaly along with an abdominal mass. An 8 day-old male baby who had a congenital abdominal mass, showed signs of heart failure and disseminated intravascular coagulation with thrombocytopenia, which were the features of Kasabach-Merritt syndrome, and the laboratory data were hemoglobin 8.3gm/dl, platelet 131,000/mm^3, prothrombin time 12.5% , activated partial thromboplastin time 200 seconds, and fibrinogen 60mg/dl. He died at 8 days of age.

In four cases surgical resection was performed, and in the case of Kasabach-Merritt syndrome, an autopsy was conducted.

Pathological Findings

In all cases, the lesions were well circumscribed and predominantly solid. They weighed 31 to 302 gm, and the cut surfaces were of variegated appearance along with foci of necrosis, hemorrhage, cystic change and calcification in 4 cases(Fig. 1).

Microscopically, these lesions consisted of numerous vascular channels of varying size, separated by intervening fibrous stroma. The vascular channels were either irregularly dilated or of compressed appearance and were lined by a single layer of flat or occasionally plump endothelial cells with an innocuous cytologic appearance(Fig.2). Both the endothelial and intervening elongated cells were devoid of mitotic activity and nuclear anaplasia. The number and size of the vascular channels varied area by area. Reticulin staining demonstrated that the tumor cells were endothelial cells on the luminal side of the vascular reticulin sheath. The sections taken from the central portions showed fibrosis and necrosis due to infarction resulting from vascular thrombosis in most cases. Focal calcification and hemosiderin deposits were also noted. Foci of vascular conglomerations reminiscent of cavernous hemangioma were occasionally found. Small bile ducts were often seen in the fibrous stroma, mainly at the periphery of the mass. The tumor cells lining the luminal border of the vascular space were positive to factor VIII-related antigen on immunohistochemical staining (Fig. 3).

Electron Microscopic Findings

The clinicopathological findings of 5 cases are summarized in Table 1, and in 3 cases (case I, case 4 and case 5) ultrastructural examination was performed. Ultrastructurally, case 1 showed plump polygonal to spindle-shaped cells forming variable-sized lumina surrounded by sparsely arranged elongated spindle cells. The cytoplasmic borders of the inner cells were closely joined with scattered desmosome-like tight junctions

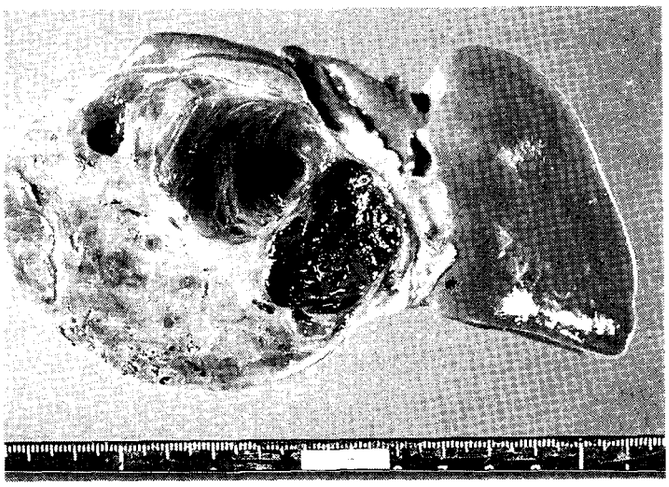

Fig. 1: A well circumscribed, brownish solid tumor with areas of necrosis and hemorrhage replacing most of the right lobe of the liver.

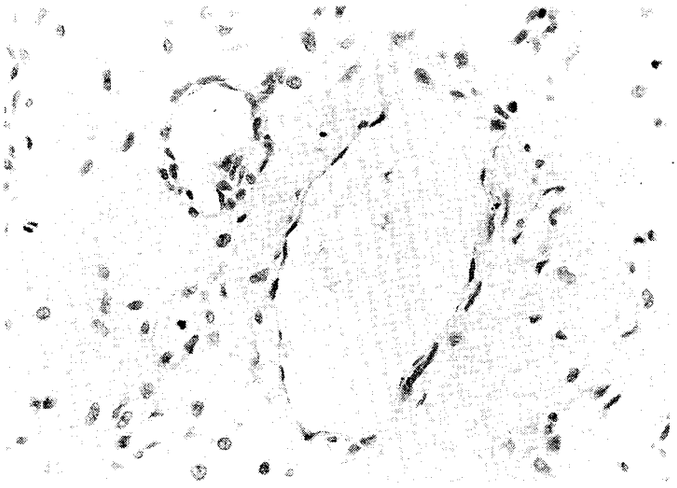

Fig. 3: Positive immunostaining using ABC method to factor VIII-related antigen (ABC method, × 200).

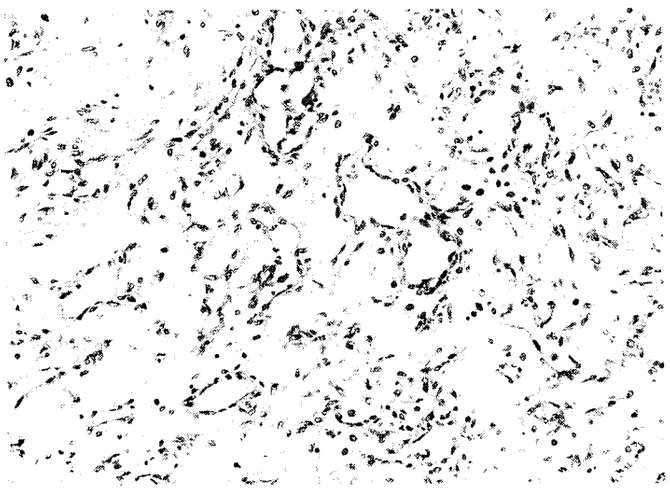

Fig. 2: Vascular channels of varying size separated by intervening fibrous stroma(H&E, × 100).

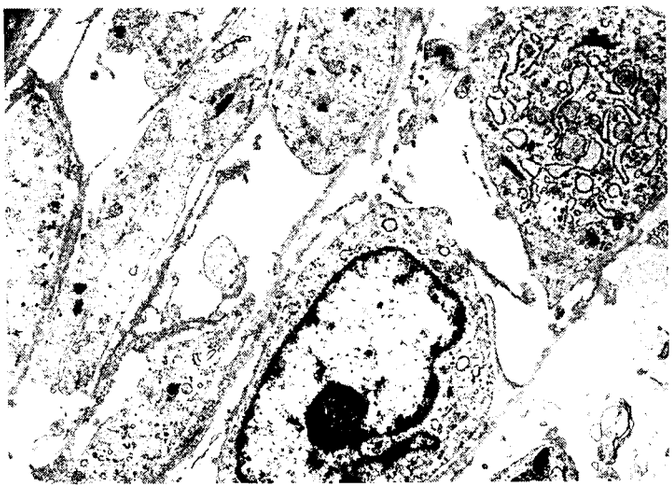

Fig. 4: A pericyte, beneath the basal lamina of a vascular lumen, having scanty cytoplasm and a large ovoid nucleus(× 15,000).

and lined continuously with basal lamina of variable thickness. The content of the cytoplasm included plentiful fine filaments with characteristic arrangement, RERs, poly-ribosome, and occasional pinocytotic vesicles. There were a few Weibel-Palade bodies, seen in all cases examined. The nuclei of the neoplastic endothelial cells were ovoid to polygonal, with a slight convolution, and the nucleoli were single and prominent. The chromatin showed peripheral linear condensation and sparse pattern. Sparsely arranged spindle cells showed elongated bipolar cytoplasm which contained abundant filaments with many focal densities, free ribosomes, and dense plaques in the membranes. Basal lamina was well developed around the cytoplasmic membrane. In case 4, the tumor cells showed numerous irregular fine cytoplasmic processes along the luminal surface and were surrounded by discontinous basal lamina and pericytes(Fig. 4). Tumor cells had large numbers of cytoplasmic organelles including fine filaments, pinocytic vesicles, Weibel-Palade bodies, RERs and mitochondria. Intervascular spaces contained abundant collagen fibers. In case 5, the tumor was composed of endothelial cells with

Table 1. Clinicopathological summary of 5 cases

Case	1	2	3	4	5
Age at Diagnosis	6 months	40 days	30 days	3 months	8 days
Sex	Female	Female	Male	Male	Male
Duration of Symptoms	4 months	20 days	28 days	40 days	8 days
Symptoms	Abdominal mass	Abdominal mass	Abdominal mass jaundice	Abdominal mass	Abdominal mass Kasabach-Merritt syndrome
EM study		+		+	+

prominent nuclei and abundant cytoplasm. They formed vascular spaces in small areas but more often were singly scattered within the loose mesenchymal stroma showing a larger number of organelles than their normal counterparts, including abundant RERs, mitochondria, glycogen particles, and pinocytotic vesicles mainly at the luminal surface. The vascular lumen was continuously lined by basal lamina and focally protruded by the endothelial cells with intercellular tight junctions in some areas. Abundant stroma consisted of mucopolysaccharide, collagen fibrils and fibroblasts, showing prominent microcystic change. There were a few pericytes seen beneath the basal lamina of the vascular lumen, showing scanty cytoplasm and large ovoid nucleus.

DISCUSSION

The evaluation of an hepatic mass in infancy and early childhood often poses complicated diagnostic problems because of the pathologically divergent nature of primary hepatic neoplasm in this period. Among the primary hepatic neoplasms in infants and children, epithelial tumors such as hepatoblastoma or hepatocellular carcinoma and vascular tumors are known to be more frequent(Weinberg and Finegold 1983). Infantile hemangioendothelioma is the most common vascular tumor and its pathobiological behaviour is similar to that of cutaneous hemangiomas including spontaneous regression (Nguyen *et al.* 1982; Duchman *et al.* 1983), thus the differentiation of this relatively frequent vascular tumor from other malignant tumors is essential. In clinical aspects, about a half of the cases manifest within the first six weeks of life, and girls are more frequently affected(Dehner and Ishak 1971). In the present study, 4 of 5 cases were found to have tumors within 6 weeks of age, but female preponderance was not observed possibly due to the limited number of cases. Kasabach-Merritt syndrome was present in one case, and another case had jaundice. In the remaining cases, abdominal mass was the chief presenting symptom. The high output cardiac failure due to shunting through vascular tumors in the liver is a well known complication and this can be a cause of non-immune fetal hydrops(Skopec and Lakatua 1989). The useful radiologic studies described are abdominal plain films, ultrasound, CT scan, nuclear imaging and arteriography(Duchman et *al.*, 1983), and the hemangioendothelioma has characteristic CT scan findings, as well-circumscribed round or oval homogeneous masses with or without calcification. In contrast imaging, the tumors enhance to a greater degree than normal liver, and the radiological differential diagnoses are abscess, focal nodular hyperplasia, cystic mesenchymal hamartoma, hepatoblastoma and metastasis

(Lucaya *et al.* 1985). In all the cases of the present study, the tumors were observed as a well-defined mass on CT and ultrasonography.

Dehner and Ishak(1971) described two histologic types in infantile hemangioendothelioma of the liver; Type 1 was characterized by irregularly dilated and small compressed vascular spaces lined by a single layer or less often, by several layers of plump endothelial cells with an innocuous cytologic appearance, and type 2 was more aggressive in appearance and was typified by irregular budding and branching structures. Histopathologically, our cases were all type 1 hemangioendotheliomas, composed of proliferating small vascular spaces that are lined by plump endothelial cells, but there seems to be no significance in separating the two types because the findings are often overlapping, nonspecific and have no clinical significance. In the histopathological aspects, the infantile hemangioendothelioma must be distinguished from angiosarcoma and mesenchymal hamartoma (Suh et al. 1987). The former is basically a disease of adults with a higher degree of cellular pleomorphism, and a lack of regressive changes such as calcification and fibrosis, however, mesnechymal hamartoma can occur in children under two years of age. In mesenchymal hamartoma, bile ductules are usually dysmorphic and the vascular endothelial cells are flat and of compressed appearance. It has been reported that the degree of expression of factor VIII-related antigen correlates with the degree of maturation of endothelial cells(Mukai *et al.* 1980), but obvious differences in staining pattern were not observed among our cases. Besides factor VIII-related antigen, von Willebrand factor, Ulex europaeus I lectin, vimentin, actin, and thrombomodulin expression have been detected immunohistochemically in infantile hemagioendothelioma of the liver(Yasunaga *et al.* 1989), and the expression pattern differed according to the histological features of the tumors.

Ultrastructurally, the following cell types were consistently found: endothelial cells, pericytes, and interstitial cells. Endothelial cells were plump, sometimes to the point of nearly obliterating the capillary lumen, and frequently displayed bundles of intracytoplasmic filaments. They were joined to each other by typical tight junctions. Weibel-Palade bodies were found in all cases although the number varied greatly. The above findings coincided well with those of previously described cases(Balazs et al. 1978; Feldman *et al.* 1978; Gonzalez-Crussi and Reyes-Mugica 1991).

Though all the cases except an autopsy case were treated by surgical excision in our study, the therapeutic strategy for this neoplasm is still controversial. The previously reported cases had excellent prognosis after surgical resection, corticosteroid therapy, symptomatic care only or even without treatment case by case (Nguyen *et al.* 1982; Guzzetta and Randolph 1989), but surgical removal seems to be better for localized lesions, because there have been sporadic cases that have shown malignant transformation into angiosarcoma instead of spontaneous regression as in most cases (Dehner and Ishak 1971).

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