Primary Liver Tumors in Infancy and Childhood

—6 Cases Report—

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ABSTRACT

During 11 year period from 1958 to 1969 six cases of primary liver tumor under the age of 16 were encountered.

According to the histologic pattern, 3 of them were diagnosed as hepatocarcinoma, 2 as mixed hepatoblastoma, and 1 as epithelial hepatoblastoma. The three cases of hepatocarcinoma were all male, with ages of 16, 16, and 13 years respectively. On the other hand, all three cases of hepatoblastoma were under 2 years of age, namely, $1^{1/2}$, $1^{2/3}$, and $4^{1/2}$ years, and one of them was female. The clinical and laboratory findings were not characteristic enough to distinguish the two types of tumors except the age distribution. A review of the literature was made, and it was stressed that hepatoblastoma has better prognosis than hepatocarcinoma.

INTRODUCTION

Malignant tumors in infancy and childhood mainly arise in the hematopoietic and central nerve systems, kidney, adrenal gland and bone and sarcoma has been known to be more common than carcinoma. In contrast to adulthood, the site, growing rate and the histologic pattern of malignant tumors in prepuberty are quite different from each other. The diagnosis, management and prognosis of these tumors are to be given attention. Furthermore the position of malignant tumor in pediatric field must be stressed because the death due to malignant tumor has increased day by day. (Stowen,1966)

Primary hepatomas also arise in the adult but rarely in pediatric age, of which Steiner (1938) reported 77 cases and on histologic peculiarity of which Milman and Grazel (1951) studied. Until recently no verified differences between the hepatomas of adults and children have been established but there are references that surgical resection (Ishak & Glunz, 1967; Martin et al., 1969) or administration of anticancer agents (Lascari, 1970) may give better survival in cases of hepatoblastoma which has definite histopathologic characteristics. Therefore the classification based on the morphology of primary liver tumor becomes the subject of this problem.

In Korea, although it is stated that primary hepatic carcinoma in adults is relatively common, primary liver tumor in infants and children is very rare and until now only 5 cases have been reported, three of which reported by Lee (1962), one by Rhim (1965) and one by Joo and Kim (1968), and only one was classified as mixed embryonal carcinoma his-
Having collected six cases of primary liver tumor under the age of 16, for the 11 years from 1958 to 1969, which were diagnosed by the Pathology Department of Yonsei University College of Medicine, we have attempted to make an association between the clinical findings and the histological classification and also have made a review of the literature.

**REPORT OF CASES**

Six cases of primary liver tumor in infancy and childhood were collected from 1958 to 1969 and their clinical and laboratory findings were summarized in Table 1.

Following are the brief descriptions of the morphology of the six cases.

**Case 1.**

Tissue was obtained by needle biopsy. The section disclosed that the neoplasm was mostly composed of anaplastic cells which showed tubular or acinar but partly trabecular patterns. Trabeculae and acini were separated by endothelial cell-lined sinusoidal spaces. Stromal proliferation was absent except at the boundary of the tumor. The margins of the tumor cells were distinct and polyhedral. The cytoplasm of the cells was heavily basophilic and granular. There was no evidence of bile stasis or giant cell formation. The non-neoplastic hepatic lobules showed somewhat increased connective tissue with proliferation of bile ducts and inflammatory cell infiltration. The final diagnosis was made then as hepatocellular carcinoma with postnecrotic type of cirrhosis.

<table>
<thead>
<tr>
<th>No. of case</th>
<th>Age</th>
<th>Sex</th>
<th>Hepatomegaly</th>
<th>Duration</th>
<th>Other complicating feature</th>
<th>Weight kg</th>
<th>Hb. gm %</th>
<th>Serum protein gm %</th>
<th>Serum bilirubin mg %</th>
<th>Serum cholesterol mg %</th>
<th>Alkaline phosphatase</th>
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<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>M</td>
<td>4 finger breadth below costal margin</td>
<td>2mo.</td>
<td>Right upper abd. pain &amp; mild tenderness</td>
<td>27</td>
<td>9.8</td>
<td>7.3 (4.7)</td>
<td>0.4 (0.2)</td>
<td>243</td>
<td>8.1 B.U</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>M</td>
<td>3cm above the umbilicus</td>
<td>8mo.</td>
<td>Epigastric distension &amp; discomfort. Petechia at anterior upper chest.</td>
<td>38.7</td>
<td>11.2</td>
<td>6.8 (4.3)</td>
<td></td>
<td></td>
<td>189</td>
</tr>
<tr>
<td>3</td>
<td>11/12</td>
<td>M.</td>
<td>Movable mass in 10mo. entire R.U.Q</td>
<td>None</td>
<td>None</td>
<td>7.5</td>
<td>9.7</td>
<td>7.1 (4.4)</td>
<td>0.6 (0.1)</td>
<td></td>
<td>2.3 S.U</td>
</tr>
<tr>
<td>4</td>
<td>3/12</td>
<td>M.</td>
<td>1 finger breadth below costal margin</td>
<td>2mo.</td>
<td>Mild splenomegaly</td>
<td>7.0</td>
<td>9.2</td>
<td>7.1 (4.4)</td>
<td></td>
<td></td>
<td>11.9 S.U</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>M.</td>
<td>3cm below costal margin</td>
<td>1mo.</td>
<td>Jaundice, epigastric pain &amp; fever</td>
<td>16.2</td>
<td>7.1</td>
<td>1.6 (4.5)</td>
<td>0.2 (0.5)</td>
<td></td>
<td>669</td>
</tr>
<tr>
<td>6</td>
<td>10/12 F.</td>
<td>10 cm. below costal margin</td>
<td>15 d.</td>
<td>Poor nutrition semicoma &amp; delayed light reflex</td>
<td>4.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

< : Direct bilirubin, mg %
* : This case has polycythemia.
** : This case died one day after admission following receiving transfusion.
( ) : Serum albumin, gm %
B.U.: Bodansky unit
S.U.: Sigma unit.
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Case 2.

Normal hepatic lobular structure were entirely disturbed. Giant trabecular pattern was most striking. Nuclei showed slight pleomorphism with giant cell formation. Central areas of some trabeculae showed necrosis and several foci of bile canalicular proliferation were also evident.

Case 3.

Tissue were obtained at laparotomy. At operation the mass was pedunculated from the left lobe of the liver. The removed mass, which was well encapsulated by relatively thick fibrous tissue, weighed 430 gm. and measured as 12.5 × 10.0 × 6.0 cm. The cut surface seemed to be somewhat hypervascularized and necrotic at some foci. Some parts of the tumor were hard and greyish-white giving the impression of osteoid tissue. The microscopic sections revealed neoplastic cell nests which were separated by proliferating mesenchymal tissue septa and an acidophilic osteoid matrix. Tumor cells were mainly fetal type which were uniformly small but had marked acidophilic cytoplasm and were aligned as trabeculae, acini, or cords. The cytoplasm of some tumor cells were vacuolated representing the so called “light and dark pattern”. Cells considered as embryonal, which were more poorly differentiated, were scattered especially within the osteoid matrix. Hematopoietic activity could be also recognized in a few areas. The final diagnosis was mixed type of hepatoblastoma.

Case 4.

There was no demonstrable mesenchymal proliferation. The section consisted of only fetal type cells and hematopoietic activity was also noted. This case was diagnosed as an epithelial type of hepatoblastoma.

Case 5.

Exploratory laparotomy disclosed numerous nodular masses diffusely scattered in the entire liver. Following biopsy 5-fluorouracil was administered without improvement of symptoms. Generally, the histologic section was similar to that of the second case, but cirrhosis was questionable and cellular pleomorphism was striking.

Case 6.

The specimen was obtained through autopsy. At postmortem examination, approximately 500 cc of blood filled the peritoneal cavity and the main lesion was limited to the liver and lungs. The liver weighed 650 gm and a 7 cm (in diameter) sized tumor, which was relatively well demarcated, was identified at the middle portion of right lobe of the liver. And the left lobe was ruptured. The microscopic features were similar to that of case 3, but marked increase of periportal connective tissue with proliferation of primitive bile ducts and parenchymal fatty change were added. The pathologic diagnosis was hepatoblastoma mixed type associated with biliary cirrhosis with metastases to left lobe of the liver and both lungs.

DISCUSSION

Concerning the primary hepatic carcinoma in infancy and childhood, Steiner (1936) had already reported on the clinical features of 77 acceptable cases including two of his own. Bigelow and Wright (1953) reported 95 cases collectively and stressed that primary hepatic tumor occurred in infancy and childhood with sufficient frequency that possibility of their occurrence should be considered in the differential diagnosis of right sided abdominal masses.

Although considerable number of additional case reports have been appeared, McDougal and Catzmos (1957) could collect only four cases of primary hepatic tumor among 2,000
autopsies during 23 years in Indiana Univ., and only eleven cases of the liver carcinoma below the age of 16 were compiled by Shorter et. al. (1960) who reviewed the records for 53 years in Mayo Clinic. Anyhow the incidence of primary hepatic tumor in prepubertal age seems to be extremely rare.

It had been considered as an interesting phenomena that most of the reported cases were from Europe and America where the adult hepatoma was relatively rare, while only a few cases reported from where adult hepatoma occurred in high incidence (Edmondson, 1958). But Watanabe and Lobayashi (1961) stated that more than 40 cases with primary hepatic tumor in Japanese children had been reported in the Japanese literature since 1911, and they reviewed their 19 new cases. Besides, Kasai et al. (1967), Lin et al. (1966) and Muir (1961) presented several cases independently in Japan, Taiwan and Singapore, respectively.

Meanwhile we have collected 6 cases of primary liver tumor under 16 years old, five of which had been diagnosed through needle or open biopsy and one through postmortem examination, since 1958 to 1969, while 13 cases of Wilm's tumor of this age group were recorded during same period.

Among 77 cases tabulated by Steiner (1938), 68% occurred in male, 53.2% were before the age of two years and inciduous enlargement of the abdomen was the most apparent symptom, and if not complicated, jaundice and ascites were uncommon. The average survival time after the appearance of symptom was four months even with surgical intervention. Like in adulthood, according to him, primary hepatic carcinoma of infants and children arose mostly from hepatic parenchymal cells with a few exceptions which were from bile duct cells. But metastasis was present in 27.2% of cases of the children reviewed, as compared with 66% of Eggel's cases of adults.

Bigelow and Wright (1953) also stated that the first recognizable sign in hepatoblastoma was usually the gradual enlargement of the abdomen with the development of a palpable mass in the upper right abdomen, and anorexia, loss of weight and anemia occurred frequently but jaundice and ascites were not common.

Milman and Grazer (1951) reviewed the literature and collected 27 cases under the name of "mixed tumor" which was composed of elements from more than one primary germ layers. Excluding one case which was considered as benign and other 6 cases which had no mention whether benign or malignant, they seemed to align the remaining 20 cases as malignant. Of these, 67% were under 8 years of age at the time of diagnosis so they emphasized that this group of primary hepatic tumors had different features from hepatocarcinoma morphologically.

To make a distinction from the mixed tumor of the salivary gland, Edmondson (1958) asserted that it should be termed "hepatic mixed tumor" and malignancy must be distinguished from benign, although whether the latter was truly benign or not.

Since then, embryonic tumors arising in the liver were classified into 1) embryonic hepatomas which containing only embryonic liver tissue, 2) mixed hepatoblastomas containing not only mesenchymal but also osteoid and cartilaginous tissues, and 3) rhabdomyoblastic mixed tumors, by Willis (1960, 1962) who believed them to be highly malignant. Although Peterson et al. (1961) presented a case of more than 5 year survival after surgically removing an embryonic hepatoma, such classification had not been widely utilized. Forty-seven cases of
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primary liver tumor registered with the Registry of Pediatric and Hepatic Pathology of the Armed Forces Institute of Pathology had been subjected for Ishak and Glunz (1967) to divide primary liver tumor of infancy and childhood into hepatocarcinoma and hepatoblastoma for clinical and pathological benefits. The hepatoblastoma was subdivided into epithelial type and mixed type, and the validity of such clarification were indicated by Ito and Johnson (1969) who observed the fine structure of the tumor cell, and were supported clinically by Martin and Woodman (1969).

According to the study of Ishak and Glunz (1967), hepatocarcinoma occurred after 5 years of age and affected males eleven times more common than females. On the other hand for hepatoblastoma, although males predominate, the ratio was only 2.5:1 and was found under the age of 2 years. Progressive enlargement of the abdomen and palpable mass were common in both types of hepatoma, however, abdominal pain or discomfort and weight loss were more evident in hepatocarcinoma. Pallor was observed in one third of the patients with hepatoblastoma, in contrast with hepatocarcinoma in which it was not a presenting sign. Furthermore, of the 18 cases with hepatoblastoma, 9 were alive and well up till the time of publication after surgical remove, resection of the tumor or lobectomy, especially 6 cases survived for four to thirteen years. But the average survival in the patients with hepatocarcinoma was 6.6 months in spite of best management including surgical removal.

Hepatoblastoma had a tendency to be rather solitary. However, microscopically the epithelial type of hepatoblastoma was composed of fetal type cells similar to the hepatic cells of prenatal fetus and more undifferentiated embryonic cells. Both types of cells were much smaller than those of normal liver cells and showed little or no pleomorphism and giant cell formation. In many of the cases extramedullary hematopoiesis was observed but association with cirrhosis was not identifiable in any epithelial type of hepatoblastoma. Mixed hepatoblastoma usually contained, in addition to the above epithelial components, mesodermal elements, and osteoid tissue was common.

Using their classification, our 3rd and 6th cases and the 3rd case documented by Lee et al. (1962) were considered as mixed type of hepatoblastoma, and our 4th case was an epithelial type, although it is difficult to completely rule out the possibility of a mixed type because the specimen of the latter case was obtained by needle biopsy. Our three cases of hepatoblastoma and of Lee’s one (1962) were all under the age of 2 years, and $1/_{18}$, $1/_{16}$, $1/_{12}$, and $1/_{10}$, respectively. On the other hand, 7 cases of hepatocarcinoma were exclusively male with a late age of onset (Table 2).

Another point of interest indicated by Ishak and Glunz (1967) as one of the differential points is that cirrhotic change may be associated with hepatocarcinoma but not with hepatoblastoma.

Histologic sections of our 2nd case and one of Lee’s showed postnecrotic cirrhosis with hepatocarcinoma and last one of ours revealed hepatoblastoma associated with the biliary type of cirrhosis.

Edmondson (1958) presented mixed hepatic tumors which were combined with biliary cirrhosis, and Deoras and Dicus (1968) reported one case of hepatocarcinoma with congenital biliary stenosis.

In spite of the fact that Ishak and Glunz (1967) enumerated the associated syndromes with epithelial carcinoma of the liver in infancy and childhood, we could not identify the
specific agreement.

Willis, (1960, 1962) considering the histogenesis of hepatoblastoma, suggested that it is not but teratogenic and originates from primitive hepatic blastema. But regarding that the appearance of the tumor even early in the fetal life, Ishak and Glunz (1967) inferred that the features of hepatic tumor were related to the stage of oncogenesis, i.e. the composition of hepatoblastoma may be different with the stage, and teratoma may possibly occur if the oncogenic insult occur very early. And although Schiödt (1970) recently asserted its ectodermal origin, it still has remained controversial.

McDonald (1967) and Fredens (1969) stressed on the importance of angiography, and Fish and McCary (1966) emphasized surgical treatment, however, because study on a significant number of cases still has not been carried out, the age difference seems to be most reliable for the clinical distinction of hepatoblastoma and hepatocarcinoma. Martin and Woodman (1969) reported surgical cure in hepatoblastoma and Lascari (1970) presented a four months old patient with hepatoblastoma that remained well for 2 years after vincristine sulfate. But the treatment and prognosis of this neoplasm must be given further study. Unfortunately, since our cases were not followed up, the prognosis could not be ascertained.

In summary pathological classification of hepatoblastoma and hepatocarcinoma is very important in view of their great difference in prognosis.

REFERENCES


Fish, J.C. and McCary, R.G.: Primary cancer of

Table 2. Primary hepatic tumors in infancy and childhood reported in Korea

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Reporter</th>
<th>Sex</th>
<th>Age</th>
<th>Osteoid and/or mesenchymal tissue</th>
<th>Extramedullary hematopoiesis</th>
<th>Cellular pleomorphism</th>
<th>Cirrhosis</th>
<th>Diagnosis</th>
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<td>F</td>
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</tr>
<tr>
<td>2</td>
<td></td>
<td>M</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>hepatocarcinoma</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>M</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>4</td>
<td>Rheem, 1965</td>
<td>M</td>
<td>1/12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Joo &amp; Kim, 1968</td>
<td>M</td>
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<tr>
<td>6</td>
<td>Present report</td>
<td>M</td>
<td>16</td>
<td>-</td>
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<td>+</td>
<td>hepatocarcinoma</td>
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<td>7</td>
<td></td>
<td>M</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>hepatocarcinoma</td>
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<tr>
<td>8</td>
<td></td>
<td>M</td>
<td>1/12</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>hepatoblastoma, mixed type</td>
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<tr>
<td>9</td>
<td></td>
<td>M</td>
<td>1/12</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>10</td>
<td></td>
<td>M</td>
<td>13</td>
<td>-</td>
<td>-</td>
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<td>±</td>
<td>+</td>
<td>hepatoblastoma, mixed type</td>
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</tbody>
</table>
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the liver in childhood; A review with emphasis on treatment and survival. Arch. Surg. 93:355, 1966.


Fig. 1. Hepatocarcinoma (Case 1). Endothelial cell-lined sinusoidal spaces separate the acini or tubules composed of the neoplastic cells. Hematoxyline & eosin stain, ×430.

Fig. 2. Hepatocarcinoma (Case 2). Neoplastic cells are arranged in giant trabecular pattern and the trabeculae are separated by endothelial cell-lined sinusoidal spaces. Hematoxyline & eosin stain, ×430.

Fig. 3. Hepatoblastoma, mixed type (Case 3). This section shows nest of fetal type neoplastic cells, osteoid tissue and proliferation of mesenchymal connective tissue. Hematoxylin & eosin stain, ×100.
Fig. 4. Hepatoblastoma, epithelial type (Case 4). This section shows relatively monotonous small neoplastic cells of the fetal type. Hematoxyline & eosin stain, ×430.

Fig. 5. Hepatocarcinoma (Case 5). Neoplastic cells show marked pleomorphism, formation of giant trabeculae and numerous giant cells. Hematoxyline & eosin stain, ×430.

Fig. 6. Hepatoblastoma, mixed type (Case 6). This section shows embryonal type, neoplastic cells, osteoid tissue and fibroblastic proliferation. Hematoxyline & eosin stain, ×100.