Teratoid Hepatoblastoma: Multidirectional Differentiation of Stem Cell of the Liver

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Hepatoblastoma is the most common malignant hepatic neoplasm of childhood, showing a wide spectrum of epithelial and mesenchymal components. Teratoid hepatoblastoma, which reveals multiple lines of tissue differentiation such as mucinous epithelium, melanin pigment, endocrine differentiation, glial and mesenchymal components, has rarely been observed. We report a case of teratoid hepatoblastoma in a 22-month-old girl. She had been diagnosed with hepatoblastoma through percutaneous needle biopsy of the liver and treated with 10 chemotherapy cycles of epirubicin, VP-16 and cisplatin and with hepatic artery embolization. After 10 months, an extended left lobectomy was performed. Grossly, a multinodular, partly well-demarcated, solid mass (7 × 5 cm) with dense fibrosis and focal cystic change occupied almost the entire specimen. There was extensive necrosis due to preoperative treatment. Microscopically, the tumor showed multiple lines of differentiation, which was composed of embryonal, fetal hepatocytes and mesenchymal elements with numerous foci of osteoid. There were also other components showing endodermal, neural, melanocytic and endocrine differentiation. These teratoid components were considered relatively resistant to preoperative chemotherapy, in contrast to extensive necrosis of both embryonal and fetal hepatocytes. These teratoid features of hepatoblastoma are considered to be a multidirectional differentiation of the small epithelial cells or stem cells of the tumor.

**Key Words:** Hepatoblastoma, teratoid, multidirectional differentiation, stem cell, liver, chemotherapy

**INTRODUCTION**

The hepatoblastoma, the most common malig-

**CASE REPORT**

A 22-month-old girl was transferred to our hospital in December 1997 due to an abdominal mass. The only abnormality upon physical examination was a large hard mass that was palpable beneath the right costal margin. A computed tomography of the abdomen showed a huge mass involving the right and left lobes of the
liver, which had a lobulated contour with calcification (Fig. 1). The initial laboratory test results revealed an AST of 66 IU/L, ALT of 211 IU/L, and alkaline phosphatase of 251 IU/L. The serum alpha-fetoprotein level was 418.4 IU/ml (normal 0-10 IU/ml). One month later, the alpha-fetoprotein level had increased significantly to more than 50,000 IU/ml. A percutaneous needle biopsy was performed and the pathologic diagnosis was hepatoblastoma of the epithelial type. Subsequently, the patient received 10 courses of chemotherapy using epirubicin, VP-16 and cisplatin and hepatic artery embolization. The size of the mass decreased and serum alpha-fetoprotein level decreased slightly to 16,886 IU/ml.

After 10 months, an extended left lobectomy of the liver including segments I to V and VIII was performed. During postoperative care, septic shock and necrotizing entero-colitis developed and the patient died during conservative treatment one month after surgery. An autopsy was not performed.

Pathologic findings

Gross finding: The product of the extended left lobectomy of the liver was composed of three parts, measuring 16 × 9 × 4 cm in the largest one, and weighing 200 g in total volume. The tumor measured 7 × 5 cm and the sectioned surface was reddish tan, multinodular, partly solid and partly cystic (Fig. 2). The central cystic portion, measuring 3.5 × 2.5 cm, was filled with a dark-red, hemorrhagic, friable material. There was extensive necrosis of about 40% of the tumor. The mass was surrounded by dense fibrotic rim with multifocal calcification. A small portion of the normal-looking liver was included in the specimen.

Microscopic finding: The resected tumor showed mixed epithelial and mesenchymal components and multilocular cysts (Fig. 3). Nests of hepatocyte-like epithelial cells showed fetal and
embryonal patterns (Fig. 3A). The fetal patterns were composed of uniform trabeculae of small, round-to-cuboidal cells with abundant cytoplasm and a distinct cytoplasmic membrane. The trabeculae were lined by indistinct sinusoidal lining cells. Embryonal patterns showed loosely arranged irregular and angulated cells with high nuclear-cytoplasmic ratio and indistinct cytoplasmic membrane and they frequently formed trabeculae and acini. These cells were positive for both cytokeratin 19 and albumin (Fig. 4). The cystic spaces were lined by stratified columnar or mucinous epithelium. The cells showed positive expression for cytokeratin, carinoembryonic antigen and alpha1-antitrypsin. Aggregates of the endocrine cells with eosinophilic cytoplasm were found adjacent to the cysts (Fig. 5A). These cells were immunoreactive for AE1 (low molecular weight cytokeratin) and chromogranin (Fig. 5B). Numerous dark brown pigmented cells were also found (Fig. 5C), and they were positive for HMB45 and the fine dark brown granules were stained for Fontana-Masson stain (Fig. 5D). The areas of eosinophilic fibrillary appearance (Fig. 6A) were positive for glial fibrillary acidic protein (Fig. 6B) and focally for synaptophysin (Fig. 6C), which suggested neural and glial differentiation. Extramedullary hematopoiesis was not distinct. The mesenchymal elements were dispersed in the mass and they were composed of spindle cells with loose and slightly myxoid tissue. Numerous foci of osteoid formation were present and some of them were partially calcified. The lacunar cells of osteoid material showed osteoblastic differentiation. The non-neoplastic liver surrounding the mass showed ductular proliferation and fibrosis with chronic inflammatory cell infiltration.

**DISCUSSION**

Hepatoblastoma resembles the embryonic-fetal liver.\(^5\) According to the histologic classification of hepatoblastoma by Stocker,\(^2\) the tumor can be divided into six patterns which are based on the combination of the epithelial component and the presence or absence of mesenchyme and teratoid features. Teratoid hepatoblastoma, which displays multiple lines of differentiation, demonstrates a spectrum of morphologic features that challenge the definition of both hepatoblastoma and teratoma.\(^3\)

The hepatic stem cells, referred to as ‘small cells’ or ‘small epithelial cells’, are primitive cells with the abilities of proliferation, self-maintenance and the production of a large number of differentiated functional progeny. They show similar immunohistochemical and ultrastructural features to those of the oval cells of rodents.\(^7\) Small epithelial cells and oval cells are both immunoreactive for the marker of biliary differentiation of cytokeratin,\(^7\) and the marker of hepatocytic differentiation of albumin. These cells have been considered to be the origin of the hepatoblastoma,\(^3,11\) and they are also found in the presenting case.

The characteristic feature of the presenting case is teratoid differentiation, including intestinal type epithelium and tubules lined by clusters of cells of endocrine differentiation, melanin-containing cells, and cells of neuronal and glial differentiation. Such teratoid features have been reported in several cases of hepatoblastoma,\(^3,7\) although they are not components of the normal liver. Recently, it is reported that purified hematopoietic stem cells can differentiate into hepatocytes in vivo and these cells have extraordinary plasticity, which can differentiate into blood vessel, muscle and neural tissue.\(^13\) It is postulated that various elements of teratoid hepatoblastoma might be derived from the multiple lines of differentiation of multipotent or less committed stem cells. Rodent hepatic tumors, which are transformed from rat oval cells, have been reported to demonstrate intestinal epithelial and mesenchymal differentiation as well as hepatocytic and biliary differentiation.\(^9\)

This patient received 10 cycles of chemotherapy before operation and it may have provoked a differentiation of the less committed stem cells. The differentiation of blastemal tissue following chemotherapy is well documented in Wilms’ tumor.\(^14\) The presenting case showed approximately 40% necrosis of the epithelial component and fibrosis with multifocal calcification due to chemotherapy. However, mesenchymal elements and teratoid components, which are relatively resistant to preoperative chemotherapy,\(^7\) were viable.
Fig. 4. Embryonal hepatoblast component of teratoid hepatoblastoma showing positive immune reaction for albumin (A) and for cytokeratin 19 (B).

Fig. 5. Endocrine and melanocytic components of teratoid hepatoblastoma. Aggregates of endocrine cells with eosinophilic cytoplasm (A) showing positive immune reaction for chromogranin (B). Numerous dark brown cells (C), intermingled with the osteoid, showing black pigments stained by Fontana-Masson stain (D).

Fig. 6. Neural and glial differentiation in teratoid hepatoblastoma. The areas of eosinophilic fibrillary appearance (A) are positive for glial fibrillary acidic protein (B) and focally positive for synaptophysin (C).

In conclusion, we report a case of teratoid hepatoblastoma that demonstrated multidirectional differentiation of small epithelial cells or stem cells of the liver.

REFERENCES


