

Hepatoblastoma with pure fetal epithelial differentiation in a 10-year-old boy

A rare case report and review of the literature

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Abstract

Rationale: Hepatoblastoma is a rare malignant embryonal tumor that only accounts for approximately 1% of all pediatric cancers and mostly develops in children younger than 5 years old. Moreover, the occurrence of hepatoblastoma in adults is extremely rare.

Patient concerns: Herein, we present a rare case of hepatoblastoma with pure epithelial differentiation in a 10-year-old boy. Pathological examination was performed. The tumor was 15 cm × 15 cm in size with clear margins. The cut surface was multiple nodular and grey-yellow. Histologically, the small cuboidal tumor cells were arranged in trabeculae with 2–3 cell layers. The tumor cells had eosinophilic or clear cytoplasm, formed dark and light areas, and were positive for alpha-fetoprotein, CK, CK8/18, CD10, hepatocyte, and GPC3. CD34 staining revealed that the sinusoids were lined by endothelial cells in the tumor tissues. The Ki67 index was approximately 20%.

Diagnoses: Based on these findings, the case was diagnosed as hepatoblastoma with pure fetal epithelial differentiation.

Interventions: The tumor was completely removed.

Outcomes: No recurrence was found 3 months after the operation.

Lessons: Hepatoblastoma with pure epithelial differentiation can also occur in older children. Children rarely notice and report any physical abnormality, and this may be among the primary reasons for the late diagnosis of the tumor. Annual health checks may be beneficial in the detection of these rare tumors and improvement of patient outcomes.

Abbreviations: AFP = alpha-fetoprotein, HE = hematoxylin-eosin, HPF = high-power field.

Keywords: case report, fetal epithelial differentiation, hepatoblastoma, liver

1. Introduction

Hepatoblastoma is a rare malignant tumor in children and only accounts for approximately 1% of pediatric cancers,^[1] although it is the most frequent liver tumor among children.^[2] It commonly develops among children aged less than 5 years.^[2] Hepatoblastoma in adults is extremely rare, with no more than 70 cases reported by 2016.^[3] Whether this tumor actually develops among adults remains controversial.^[4] Some experts believe that the tumor reported as hepatoblastoma may be a misdiagnosis of

hepatocellular carcinoma or sarcoma. Hepatoblastomas occur more often in the right hepatic lobe.^[2] Symptoms commonly include abdominal mass, abdominal swelling, and abdominal pain.^[2] Alpha-fetoprotein (AFP) is a useful clinical marker for diagnosing hepatoblastoma, but approximately 10% of patients do not present with an elevated AFP level at the time of diagnosis.^[2] AFP was also found to play a significant role in patient prognosis.^[2] The prognosis of patients with hepatoblastoma mainly depends on the presence or absence of metastasis and if complete resection is possible.^[2] The lung is the most common site of metastasis, with approximately 10% to 20% of patients having lung metastasis at diagnosis.^[2] Adults with hepatoblastoma have poorer clinical outcomes than children.^[3] Approximately 60% of adults have massive tumors on initial diagnosis, which negatively affects the patient's outcome.^[2] Chemotherapy and transplantation can increase the chance of resection and improve clinical outcomes.^[2] Cisplatin is the most commonly used chemotherapeutic agent.^[5] Herein, we report a rare case of hepatoblastoma in a 10-year-old boy.

2. Case presentation

2.1. Clinical history

The patient was a 10-year-old boy whose parents noted a fist-sized abdominal mass in his upper right abdomen 15 days before consultation. He had occasional abdominal pain with no apparent abdominal distension. His appetite and bowel movement were normal. Liver function test showed high alanine aminotransferase (292 U/L) and low prealbumin (8.2 mg/dL) level. Blood coagulation tests only showed a slightly low level of Fg (1.99 g/L). Routine blood test showed a low level of

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hemoglobin (106 g/L) and granulocyte ratio (39.1%). AFP was not examined preoperatively, but it was high at 733 ng/mL 35 days post-op.

3. Materials and methods

The tumor samples were examined via hematoxylin-eosin (HE) and immunohistochemistry staining as described previously.^[6] The primary antibodies were CD10 (1:100, DAKO), CD34 (1:100, DAKO), CK (1:100, DAKO), CK8/18 (1:100, DAKO), CK19 (1:100, DAKO), chromogranin A (1:100, DAKO), synaptophysin (1:100, DAKO), AFP (1:200, DAKO), hepatocyte (1:100, DAKO), GPC3 (1:100, DAKO), β -catenin (1:200, DAKO), and Ki-67 (1:200, DAKO). This study was prospectively performed and approved by the institutional Ethics Committees of China Medical University and conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

4. Results

4.1. Gross findings

The tumor was located in the right hepatic lobe, and complete resection was performed. Results of gross examination of the tumor are shown in Fig. 1. The surface of the liver was smooth without obvious disruption (Fig. 1A). The tumor was approximately 15 cm \times 15 cm in size, was nodular, and had crisp texture. The cut surface was grey-yellow (Fig. 1B) with clear margins. The tumor compressed the surrounding liver tissues and formed a thin pseudocapsule. Scattered hemorrhage can be seen in the tumor.

4.2. Histopathological features

The histopathological findings are shown in Fig. 2. Dark and light areas of the tumor cells were noted (Fig. 2A), and the tumor cells formed multiple nodules that were separated by fibrous septum (Fig. 2B). Some tumor cell nests invaded the fibrous envelope (Fig. 2C). The tumor cells were cuboidal and arranged in trabeculae composed of 2 to 3 cell layers (Fig. 2D). They were relatively small and uniform in size and shape. The tumor cells also contained a small round nucleus with fine nuclear chromatin and a small nucleolus. In the dark areas, the tumor cells contained eosinophilic finely granular cytoplasm (Fig. 2E), while the light areas comprised tumor cells with clear cytoplasm (Fig. 2F). Bile stasis were found in few areas (Fig. 2G). Moreover, the tumor cells were relatively bigger and showed mild atypia in some areas (Fig. 2H). Mitosis was rare and less than 1/10 high-power field (HPF). Focal lymphocyte infiltration was seen in the portal areas of the surrounding liver tissues (Fig. 2H).

4.3. Immunophenotype

The immunostaining pattern of the tumors is shown in Fig. 3. AFP was weakly positive (Fig. 3A), while β -catenin was positive in the cell membrane of both hepatocytes (Fig. 3B) and tumor cells (Fig. 3C). CD10 staining was diffuse in the tumor cells and showed a tiny bile canaliculi between hepatocytes in the liver tissues (Fig. 3D); the structure was unclear (Fig. 3E). CD34 staining was negative in liver tissues (Figure 3F) but positive in tumor tissues (Fig. 3G), which indicated that the sinusoids were lined by endothelial cells in tumor tissues. Chromogranin A was negative (Fig. 3H), while CK (Fig. 3I) and CK8/18 (Fig. 3J) were

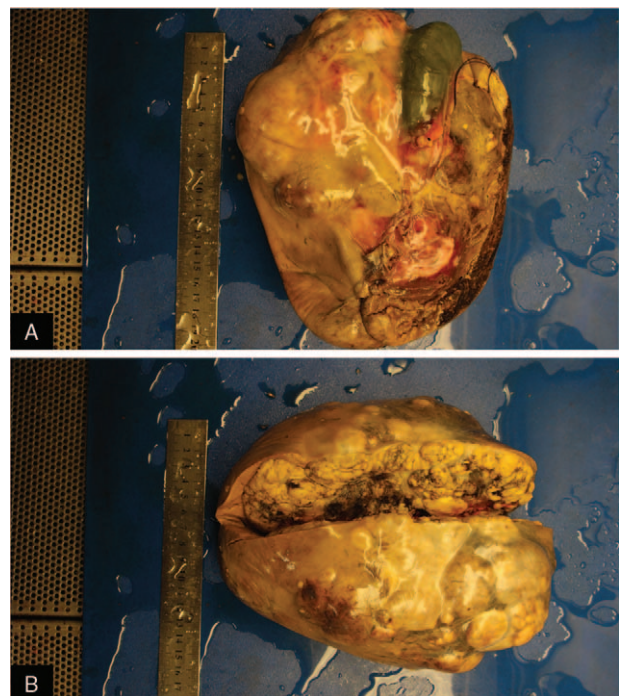


Figure 1. Gross tumor appearance. The liver surface was smooth and had no obvious disruption (A). The mass was located in the liver and was approximately 15 cm \times 15 cm in size with clear margins and thin pseudocapsule (B). The tumor was nodular, and the cut surface was grey-yellow. Scattered foci of hemorrhage can be seen inside the tumor.

positive in the tumor cells. CK19 was focally and weakly positive in the tumor cells (Fig. 3K). GPC3 (Fig. 3L) and hepatocyte (Fig. 3M) were diffusely positive in the tumor cells. Ki67 index was less than 1% in adjacent liver tissues (Fig. 3N) and approximately 20% in tumor cells (Fig. 3O). Synaptophysin was negative in the tumor cells (Fig. 3P).

5. Discussion

Hepatoblastoma is a malignant embryonal tumor that is the most frequent liver tumor among children.^[2] Most tumors develop in children younger than 5 years old.^[2] In the review by Arora^[7] of 157 patients, the age ranged from 12 to 24 months. Although rare, hepatoblastoma in adults have also been reported. Ahn et al^[8] reported a mixed hepatoblastoma composed of both epithelial and mesenchymal components in a 51-year-old female. Moreover, a review of 21 cases of hepatoblastoma in adults by the same study revealed that most tumors were mixed hepatoblastoma, and only 2 patients aged 22 and 35 years demonstrated pure epithelial type.^[8] Our patient was a 10-year-old boy, and the presence of this tumor was similarly rare when considering our patient's age.

Currently, the cause of hepatoblastoma remains unknown. Buckley et al^[9] reported that hepatitis infection was not a risk factor for hepatoblastoma. Meanwhile, maternal occupational exposure to heavy metals may be a risk factor^[9] as well as Beckwith-Wiedemann syndrome, familial history of adenomatous polyposis, and low birth weight.^[1,10,11] The pathogenesis of hepatoblastoma remains unclear.^[10] Some pathogenetic pathways found to be involved in the carcinogenesis of hepatoblastoma include the Wnt signaling pathway.^[10] In this case, we found that β -catenin was mainly expressed in the membrane of tumor cells but

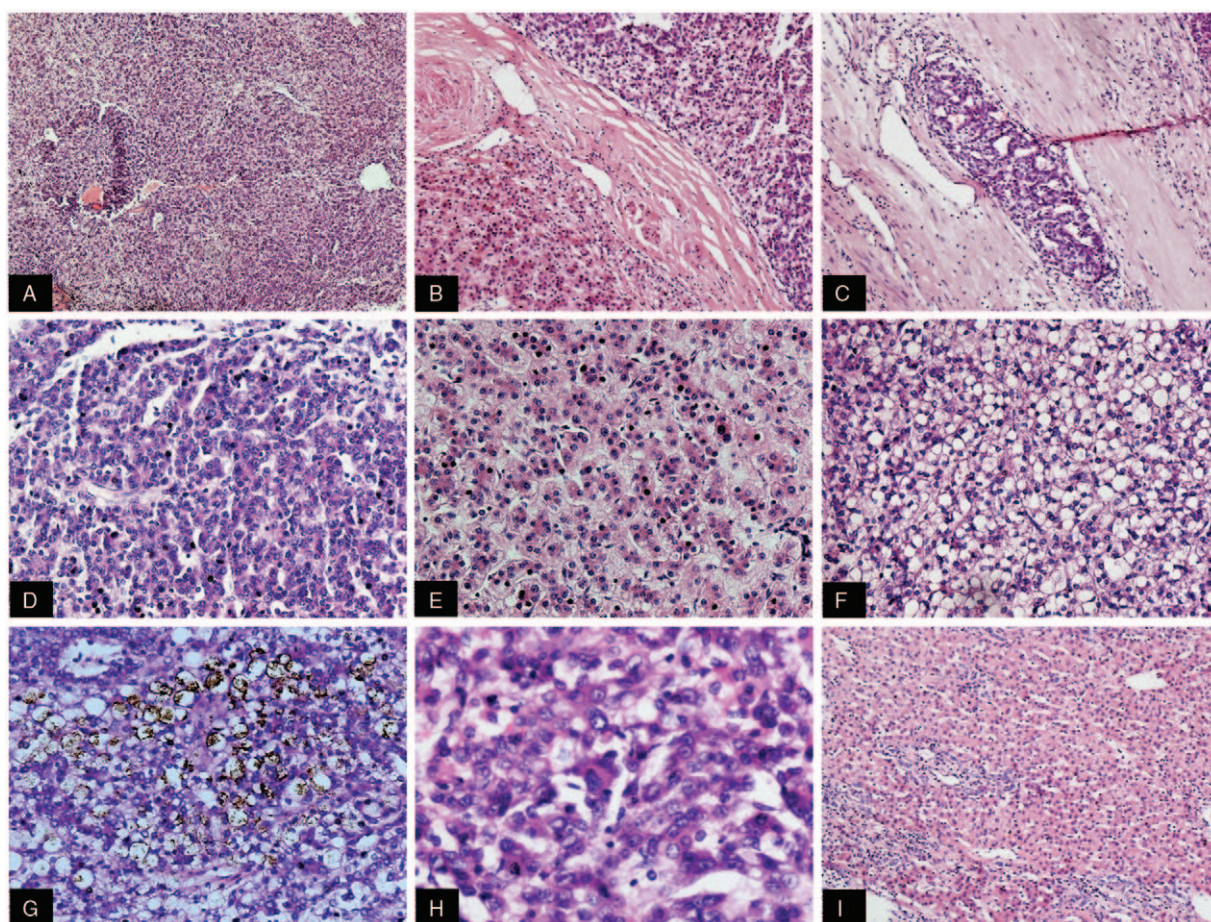


Figure 2. Histopathological findings of the tumors. The tumor tissues had dark and light areas (A). Fibrous septum was seen between the tumor cell nodules (B). Some tumor cells invaded the fibrous envelope (C). The small cuboidal tumor cells were arranged in trabeculae with 2–3 cell layers (D). The cell nucleus was small and round with fine nuclear chromatin and a small nucleolus. Some tumor cells contained fine eosinophilic granular cytoplasm that formed the dark areas (E). Tumor cells with clear cytoplasm formed the light areas (F). Bile stasis could be found in few tumor cells (G) and a few areas showed mild atypia (H). Mitosis was less than 1/10 HPF. Focal lymphocyte infiltration was noted in the portal areas of the surrounding liver tissues (I).

not the nucleus, which is common for hepatoblastoma. It does not indicate a function of Wnt signaling in these tumor cells. However, whether the Wnt signaling pathway is involved in the initial stage of tumorigenesis remains unclear.

Patients with hepatoblastoma commonly present with an abdominal mass with mild abdominal pain. AFP is an important clinical marker in both hepatocellular carcinoma and hepatoblastoma.^[12] However, like hepatocellular carcinoma, some patients with hepatoblastoma also have normal or low AFP level.^[12] In the current case, the AFP level was high 35 days post-op.

Differential diagnosis of hepatoblastoma with pure epithelial differentiation includes focal nodular hyperplasia, hepatocellular adenoma, and hepatocellular carcinoma.^[2] Park et al^[13] reported a case of hepatoblastoma that was previously misdiagnosed as combined hepatocellular carcinoma and cholangiocarcinoma in a 36-year-old woman. Focal nodular hyperplasia usually affects older children.^[2] Histologically, central or eccentric stellate scars usually exist in the tissues of focal nodular hyperplasia, which was not present in the current case.

Most patients with hepatocellular adenoma are young females, and histologically, the tumor cells are similar with normal hepatocytes. Meanwhile, the tumor cells of hepatoblastoma are relatively small and similar to the hepatocytes of a developing fetus,^[2] as in the current case. Hepatocellular carcinoma

commonly develops in adults and rarely in children. Histologically, the tumor cells of well-differentiated hepatocellular carcinoma are similar with that of normal hepatocytes. Meanwhile, the tumor cells of poorly differentiated hepatocellular carcinoma have marked atypia, which is inconsistent with the current case. CD34 and β -catenin are useful biomarkers for the diagnosis of hepatoblastoma. In hepatoblastoma, CD34 staining usually shows diffuse capillarization, which is unusual in benign lesions. Membrane β -catenin expression is common in hepatoblastoma, as in the current case.

The lung is the most common site of metastasis.^[2] Pateve reported a case of hepatoblastoma metastasizing to the lung and omentum in an 11-year-old boy, who eventually died of this cancer.^[11] The risk for metastasis is higher among adult patients with hepatoblastoma than their younger counterparts.^[4] In the report by Caso-Maestro et al,^[4] a 27-year-old patient with hepatoblastoma developed tumor recurrence in the left adrenal gland. Huang et al^[14] reported a case of metastatic hepatoblastoma in the right ventricle in an 18-year-old boy. The patient in the study by Celotti et al^[3] was a 68 year-old male who had hepatoblastoma with metastasis to the pericardium. No metastasis was detected in the current patient.

Surgery is the most beneficial treatment for hepatoblastoma.^[1,15] However, approximately 60% of the tumors cannot

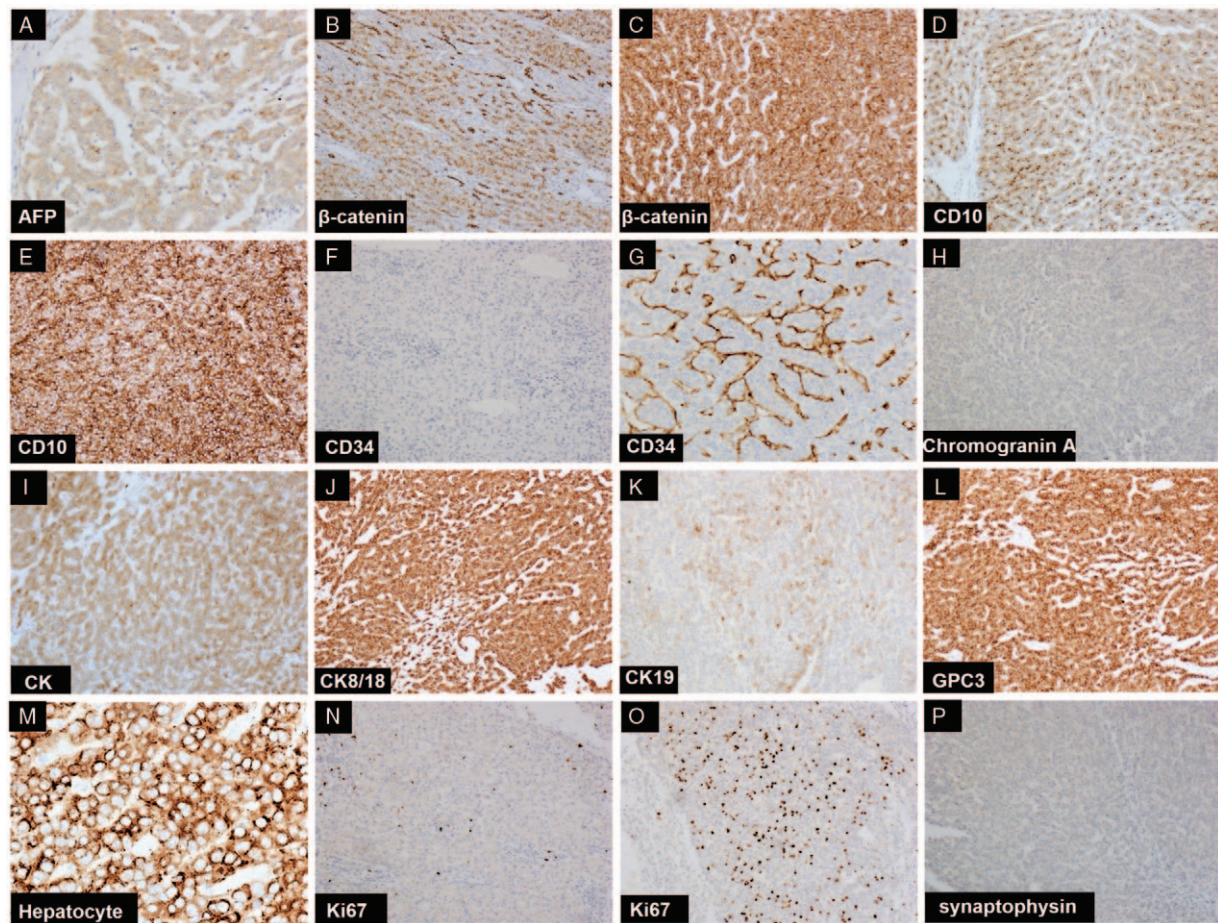


Figure 3. Immunostaining findings of the tumors. Weak AFP staining was seen in the tumor cells (A). β -catenin staining was positive in the cell membrane of both the hepatocytes (B) and tumor cells (C). CD10 staining showed a tiny bile canaliculi in the liver tissues (D). CD10 staining was diffuse in the tumor cells (E). CD34 staining was negative in liver tissues (F). CD34 staining was positive in tumor tissues (G), which indicated that the sinusoids were lined by endothelial cells in the tumor tissues. Chromogranin A and synaptophysin were negative in the tumor cells (H, P). CK19 was focally and weakly positive in the tumor cells (K). CK (I), CK8/18 (J), GPC3 (L), and hepatocytes (M) were diffusely positive in the tumor cells. Ki67 index was <1% in the hepatocytes (N) and approximately 20% in the tumor cells (O).

be completely removed because of their large size or extensive invasion.^[16,17] In the current case, the patient underwent complete tumor resection. Liver transplantation can be considered for tumors that cannot be removed by conventional surgery.^[17] Chemotherapy is an important adjuvant therapy, and cisplatin is the most commonly used chemotherapeutic agent.^[16] Preoperative chemotherapy can reduce the volume of tumors that are too big for conventional surgery.^[2,18] However, drug resistance may decrease the therapeutic effect of chemotherapy.^[19] Radiation therapy is not routinely performed for hepatoblastoma, although it has been reported to be used in some patients with unresectable tumors.^[16] The review by Schnater et al^[10] indicated that some tumors were very sensitive to radiation therapy. However, the benefit of radiation therapy in hepatoblastoma remains unclear.

6. Conclusion

The tumor was diagnosed as hepatoblastoma with pure fetal epithelial differentiation based on the clinical findings. Hepatoblastoma in patients older than 5 years is extremely rare, but our case shows that hepatoblastoma with pure epithelial differentiation can develop in older children. Children rarely notice and report any physical abnormality, and this may be among the

primary reasons for the late diagnosis of the tumor. Annual health checks may be beneficial in the detection of these rare tumors and improvement of patient outcomes.

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