Hepatoblastoma

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Abstract

Hepatoblastoma is the most common liver cancer diagnosed in children, generally presenting in children under 3 years of age. They are embryonal tumors believed to arise from a hepatocyte precursor cell and are typically heterogeneous, presenting with mixed histological patterns that may recapitulate stages of liver development. Central review of liver tumors diagnosed in children enrolled in collaborative therapeutic protocols has allowed the identification of histological subtypes with distinct clinical associations. However, and despite great therapeutic advances, the prognosis is still poor for children with unresectable or disseminated hepatoblastoma, and no biomarkers or alternative therapies are currently available. International collaborative efforts are drafting common treatment protocols, and a first consensus histologic classification is now available. New therapeutic algorithms incorporating histopathology and biological parameters, such as patient characteristics and tumor genetics, will be necessary to further improve the management and outcome of these patients in the future.

Keywords *CTNNB1*; hepatoblastoma; pathology; pediatric liver cancer classification

Introduction

Hepatoblastoma, the most common pediatric liver malignancy usually diagnosed during the first 3 years of life, is an embryonal tumor believed to arise from a hepatocyte precursor cell. Most hepatoblastomas are grossly and microscopically heterogeneous tumors displaying mixed histological patterns and cell types, which may range from well-differentiated hepatocytes to primitive undifferentiated small cells, often recapitulating stages of liver development. Treatment of hepatoblastoma usually involves a combination of surgical resection and chemotherapy and is curative for many patients. However, despite great advances in treating children with hepatoblastoma, effective therapies are still lacking for children with unresectable or disseminated disease resistant to currently available chemotherapy regimens. In addition, there are no clinical biomarkers or targeted therapies currently available for hepatoblastoma patients. Central histopathological review of hepatoblastomas diagnosed in children enrolled in pediatric collaborative therapeutic protocols has allowed the identification of histological subtypes with distinct clinical associations. Collaborative efforts to refine the first drafted consensus classification and to implement common treatment stratification systems incorporating tumor histopathology and biological parameters are currently underway. These will support therapeutic algorithms based on patient characteristics and tumor genetics, and should improve future patient management and outcome. This review highlights the most common and clinically relevant histological features and groups of hepatoblastomas, and provides an overview of recently described aspects of their biology.

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Staging of hepatoblastoma (Children's Oncology Group, USA)

I	**(a). (Favorable histology)** Completely resected with **pure fetal** histologic pattern with a low mitotic index (<2 per 10 high-power fields).
I	**(b). (Other histology)** Completely resected with a histologic picture **other** than pure fetal with low mitotic index.
II.	Grossly resected tumors with evidence of **microscopic residual**. Resected tumors with preoperative or intraoperative rupture are stage II.
III.	**(Unresectable)** Considered by the attending surgeon to be not resectable without undue risk to the patient. Includes partially resected tumors with measurable tumor left behind. Regional lymph node involvement constitutes stage III disease.
IV.	**Metastatic disease** to lungs or other organs.

Table 1

Epidemiology, clinical presentation, diagnosis and therapy

Hepatoblastoma is the most common pediatric liver cancer, representing more than 90% of malignant liver tumors diagnosed in children under 5 years of age. It usually affects young children within the first 3 years of life.[1,2] Boys are more frequently affected. Patients typically present with abdominal swelling and hepatomegaly with a sporadic single liver mass without underlying liver pathology. They are rarely congenital but may be associated with constitutional genetic abnormalities, malformations, familial cancer syndromes (Familial adenomatous polyposis, Beckwith–Wiedemann syndrome) and metabolic disorders (Glycogen storage diseases types I and IV).[3] Interestingly, several epidemiological studies have reported a recent increase in the incidence of hepatoblastoma, both in the United States and in Japan, associated with low birth weight infants[4,5] as well as other maternal and paternal environmental exposures.[6]

Accurate staging and assessment of hepatic and extrahepatic disease is of most importance. In the United States COG (Children's Oncology Group) staging includes imaging as well as surgical judgment (Table 1), while other international groups such as SIOPEL use the PRETEXT system to determine the extent of disease at the time of diagnosis.[7–9] Vascular dissemination occurs via the portal veins and hepatic veins most commonly to the lungs and regional lymph nodes, and rarely to the brain. Serum levels of alpha-fetoprotein (AFP) are very useful clinically as a hepatocellular tumor marker and marker of response to therapy, but it is not specific and needs to be used with caution in infants.[2]

Despite some discrepancies between different international therapeutic protocols, hepatoblastoma therapy generally includes a combination of surgical resection and adjuvant chemotherapy (cisplatinum based). Up-front resection and surgical staging are advised in the United States, whereas initial adjuvant therapy is strongly considered internationally.[10–14] Surgically resectable tumors are usually curable.[11,13,15,16] Multifocality, gross venous extension, distant metastatic disease,

exceptionally low (<100 mg/ml) and high (>1,000,000 mg/ml) AFP levels, are all associated with a worse prognosis, which still remains quite poor for children with non-resectable tumors, residual disease, chemoresistant tumors, or metastatic spread. Histologic differentiation is also associated with prognosis. Well-differentiated, pure fetal hepatoblastoma type with low mitotic rate is associated with a much better prognosis and can be cured with resection alone,[17] while tumors with an undifferentiated small cell component are associated with an unfavorable outcome and worse response to chemotherapy.[18,19] Other factors such as the presence of vascular invasion, proportion of surviving embryonal epithelium, extent of tumor necrosis, amount of viable mesenchymal tissue, and mitotic activity in the epithelial component, have also been reported to be of potential prognostic significance.[20,21]

Histopathology

Hepatoblastoma usually presents as a single circumscribed mass compressing the surrounding parenchyma, arising in an otherwise normal liver (Fig. 1a), and only rarely does it present as multiple nodules in cases with intrahepatic dissemination at diagnosis. The presence of underlying liver disease and cirrhosis is not seen in hepatoblastoma, but rather, is associated with hepatocellular carcinoma in more than 75% of cases. Hepatoblastomas are usually heterogeneous tumors, with 85% containing diverse elements, and a gross appearance that matches the underlying histologic components described below (Table 2). For example, the fetal component generally appears solid, soft and tan, while predominant embryonal and small-cell undifferentiated areas are grossly softer and even gelatinous. The osteoid-like component rarely calcifies, is pale and firm, and is usually more prevalent in post-chemotherapy specimens. The latter commonly display necrosis and hemorrhage.

Microscopically, hepatoblastomas are heterogeneous tumors rarely composed of only one cell type but often display combinations of epithelial, mesenchymal, undifferentiated or other components.[22,23] The most common epithelial component is the **embryonal pattern**, composed of characteristic angulated cells with high nuclear-cytoplasmic ratio, growing either in sheets or forming tubular or acinar structures, resembling the liver at 6–8 weeks gestation (Fig. 1d). Also commonly encountered is the **fetal pattern**, containing cells with centrally placed, round, small nuclei, and finely stippled chromatin, with either clear or eosinophilic cytoplasm (Fig. 1b and c) and admixed with clusters of hematopoietic precursors (extramedullary hematopoiesis).[19,24] Several studies have reported a correlation between well-differentiated fetal histology and better outcome,[15,19,25,26] particularly for pure fetal hepatoblastoma with minimal mitotic activity (less than 2 per 10 high power ×400 microscopic fields),[23] which is a surgically curable tumor. This favorable association has been documented by the most recent COG (Children's Oncology Group) protocols, with all stage I **well-differentiated fetal hepatoblastomas** with low mitotic activity being cured by surgery alone[27] (Fig. 1b). However, it is important to remember that this diagnosis requires evaluation of the complete resection specimen prior to chemotherapy, and cannot be made on biopsies. Fetal hepatoblastoma may be well-differentiated but mitotically active (also known as "crowded fetal"), which needs to be differentiated from the well-differentiated fetal pattern with low mitotic activity, as it requires chemotherapy (Fig. 1c). Hepatoblastoma tumor cells with a fetal or embryonal appearance, due to its polygonal shape and often abundant cytoplasm, may show nuclear features that are more pleomorphic (such as coarser chromatin or nucleoli), compared to well-differentiated fetal or crowded fetal patterns. This **pleomorphic epithelial pattern** is uncommon in hepatoblastoma, and more often seen in post-chemotherapy specimens and in metastases following chemotherapy, and may be difficult to distinguish from hepatocellular carcinoma when tumor cells are organized in a macrotrabecular pattern. Features of true "anaplasia", such as large cell size (3–4 times that of adjoining cells) and atypical multipolar mitoses, are rare and of uncertain significance in hepatoblastoma, but should be documented.

Neoplastic hepatoblastoma cells may occasionally show **cholangioblastic differentiation**, expressing cholangiocyte lineage markers (cytokeratins 7 and 19).[28,29] This cholangiocellular component may be situated within or surrounding the hepatocellular component of the tumor. Beta-catenin immunostaining can be very useful to differentiate this component from tubular structures found in embryonal, especially in post-chemotherapy specimens when reactive ductal proliferation is common, as neoplastic ducts usually demonstrate nuclear staining as opposed to membranous expression in benign ducts. The differential diagnosis of cholangioblastic hepatoblastoma may include other very rare so-called ductal plate tumors, pediatric intrahepatic cholangiocarcinoma, and nested stromal epithelial tumor of the liver.[30,31]

Hepatoblastomas may contain round to oval small cells (slightly larger than lymphocytes), with scant cytoplasm, fine nuclear chromatin and only minimal mitotic activity (**small cell component**). These cells may be found intermixed with other epithelial cell types, forming nests in an almost "organoid" pattern, and may be missed (Fig. 1e). Immunohistochemically, these small cells may show variable immunoreactivity for pan-cytokeratin, cytokeratins 8 and 18, and vimentin, and do not express alpha-fetoprotein.[32] In rare instances the entire tumor is composed of this small cell type **(small-cell undifferentiated hepatoblastoma)**. This group of tumors is usually diagnosed in infants and is generally characterized by low or normal serum AFP levels,[33,34] aggressive biology[18,35,36] and worse survival.[17,19,34] Recent reports have documented that at least some small-cell undifferentiated hepatoblastomas may present morphologic and biological features characteristic of malignant rhabdoid tumors, such as lack of INI1 nuclear expression,[34,37,38] and it is important to recognize this variant as these patients should be treated as malignant rhabdoid tumors rather than hepatoblastoma. A panel of immunohistochemical stains including pancytokeratin, vimentin, and glypican-3, should be used to characterize and even detect small-cell undifferentiated areas. Primary classic malignant rhabdoid tumors can also occur in the liver, with characteristic oval cells with vesicular nuclei, prominent nucleoli and paranuclear inclusions.[39,40] These INI1 negative tumors should be submitted for mutation and deletion testing, and patients screened for germline mutations (and family counseled), whenever appropriate. Fetal, embryonal, and pleomorphic epithelial cell components may display a **macrotrabecular growth pattern**, similar to that typically seen in hepatocellular carcinoma.[41] Clinical data is currently insufficient