**Hepatoblastoma**

1. An 8-month-old infant presents with a distended abdomen, and a CT of the abdomen shows a mass in the right lobe of the liver. The alpha-fetoprotein is 350,000 ng/mL. You review the case with the surgeon, who believes that the tumor is resectable, and you decide to proceed with upfront resection. Pathology shows completely resected pure fetal histology hepatoblastoma. A CT of the chest is negative, and the alpha-fetoprotein serum concentration is declining appropriately after surgery.

As you discuss the diagnosis and ongoing treatment with this infant’s parents, what would be your recommendation?

A. Observation

B. Six cycles of cisplatin-based therapy

C. Two cycles of cisplatin-based therapy

D. Intensive multiagent chemotherapy according to rhabdoid tumor guidelines

E. Radiation to the tumor bed

**Explanation**

Pure fetal histology hepatoblastoma is associated with an excellent prognosis. This histological variant accounts for approximately 5% to 10% of cases. Patients with stage I disease (as is the case for this infant) can be observed without adjuvant chemotherapy. Administration of two cycles of adjuvant chemotherapy is the recommended treatment for all other cases of stage I non–small cell undifferentiated hepatoblastoma. Intensive treatment according to rhabdoid tumor guidelines is a consideration for patients with advanced small cell undifferentiated hepatoblastoma. Radiation therapy is not commonly used in the upfront management of hepatoblastoma.

2. A 6-month-old infant presents with a distended abdomen, and imaging studies show a large unresectable hepatic mass and lung metastases. The alpha-fetoprotein (AFP) serum concentration is 80 ng/mL.

Which of the following is the most likely diagnosis?

A. Pure fetal histology hepatoblastoma

B. Conventional hepatocellular carcinoma

C. Small cell undifferentiated hepatoblastoma

D. Embryonal sarcoma of the liver

E. Fibrolamellar hepatocellular carcinoma

**Explanation**

More than 95% of primary liver tumors in patients younger than 5 years are hepatoblastomas. Small cell undifferentiated hepatoblastoma accounts for approximately 5% of hepatoblastomas, and it is associated with a worse prognosis. Clinically, a more aggressive clinical behavior and typically normal or only slightly elevated AFP characterize this variant. Molecularly, it is associated with aberrations in the *SMARCB1* gene and thus is considered a member of the rhabdoid family of tumors. Pure fetal histology hepatoblastoma presents also during the first months of life; however, it has a much more favorable clinical behavior, presenting as localized disease and with high AFP. Hepatocellular carcinoma is a tumor of older patients; the fibrolamellar variant may present in younger patients (typically in the second decade of life), and AFP may not be elevated. Embryonal sarcoma of the liver typically occurs in older children, and metastases are rare.

3. You have been asked to see a 13-month-old boy who presented with a large hepatic mass and alpha-fetoprotein serum concentration of 257,000 ng/mL. As you review the past medical and family history with the parents, which of the following familial conditions would be relevant in this case?

A. Familial hemochromatosis

B. Hereditary tyrosinemia

C. Alpha-1 antitrypsin deficiency

D. Gardner syndrome

E. Li-Fraumeni syndrome

**Explanation**

Familial adenomatous polyposis syndromes such as familial adenomatous polyposis and Gardner syndrome are associated with an elevated risk of hepatoblastoma. These syndromes are characterized by germline *APC* mutations, and the relative risk of developing hepatoblastoma is close to 800. Familial hemochromatosis, hereditary tyrosinemia, and alpha-1 antitrypsin deficiency are associated with hepatocellular carcinoma. Hepatocellular carcinoma also has been associated with Li-Fraumeni syndrome.

4. A 15-year-old previously healthy boy presents with a 3-month history of right upper abdominal quadrant pain and progressive abdominal distension. Imaging studies show a large mass originating from the liver parenchyma with lung metastases. The alpha-fetoprotein (AFP) serum concentration is 15 ng/mL.

Which of the following diagnoses would you place at the top of your differential?

A. Small cell undifferentiated hepatoblastoma

B. Embryonal sarcoma of the liver

C. Pure fetal histology hepatoblastoma

D. Epithelial hepatoblastoma

E. Hepatocellular carcinoma, fibrolamellar type

**Explanation**

More than 90% of primary liver tumors in adolescents are hepatocellular carcinoma (HCC). The fibrolamellar variant accounts for approximately 25% of HCCs, and it is typically associated with a younger age (median 12 years) and absence of preexisting cirrhosis. The serum concentrations of AFP are usually normal or only mildly elevated in fibrolamellar HCC, and patients present with a more protracted course. Small cell undifferentiated hepatoblastoma also presents with low AFP but at a much younger age, typically in the first year of life. Epithelial and pure fetal histology hepatoblastoma typically present in the first 3 years of life and are associated with high concentrations of AFP. Embryonal sarcoma of the liver usually presents in the first decade of life, and metastases are rare.

5. A 6-month-old boy presents with a large right upper-quadrant mass. Imaging studies reveal an unresectable primary liver mass with lung metastases. Alpha-fetoprotein (AFP) is 47 ng/mL. A percutaneous biopsy is performed, and tissue is sent for additional molecular studies.

What genomic alteration is likely to be found in this tumor?

A. *SMARCB1* mutation

B. *11p15.5* uniparental disomy

C. *APC* mutation

D. *Xp11* translocation

E. *CTNNB1* mutation

**Explanation**

Although *CTNNB1* is the most commonly mutated gene in hepatoblastoma, the young age of this patient, aggressive presentation, and low levels of AFP are highly suggestive of the small cell undifferentiated variant of hepatoblastoma, which is characterized by *SMARCB1* mutations. Beckwith-Wiedemann syndrome (germline 11p15 uniparental disomy) and familial adenomatous polyposis (germline APC mutations) are associated with standard embryonal histology hepatoblastoma and elevated AFP levels. Xp11 translocations are typical of renal cell carcinoma.

6. A 6-month-old infant with history of low birth weight presents for evaluation of a right upper quadrant mass. Laboratory evaluation shows alpha-fetoprotein serum levels of 358,000 ng/mL. Imaging studies show a PRETEXT-II liver mass and no lung metastases. A resection of the mass is performed, and pathology shows a completely resected pure fetal histology hepatoblastoma.

Which presenting feature is the strongest predictor of outcome?

A. Low birth weight

B. Absence of lung metastases

C. Elevated alpha-fetoprotein serum levels

D. Pure fetal histology

E. PRETEXT-II

**Explanation**

Absence of lung disease, pure fetal histology, and PRETEXT-II are all good prognostic indicators in this case. Of them, pure fetal histology is the strongest prognostic factor, and this patient could be cured with surgery only, without adjuvant chemotherapy.

7. You have been asked to see a 6-month-old infant with a new diagnosis of Beckwith-Wiedemann syndrome, and you prepare to counsel the family about cancer risk. What is the most common malignancy in these patients?

A. Adrenocortical carcinoma

B. Neuroblastoma

C. Wilms tumor

D. Rhabdomyosarcoma

E. Hepatoblastoma

**Explanation**

Children with Beckwith-Wiedemann syndrome have an elevated risk of cancer; malignancy risk is close to 10% in the first decade of life. Wilms tumor is the most common neoplasm, followed by hepatoblastoma, adrenocortical tumors, and other malignancies.

1. A 9-month-old boy has been referred to you for the evaluation of an enlarged abdomen. Imaging studies show a large liver mass (PRETEXT III). Alfa-fetoprotein is 98 ng/mL, and a CT scan of the lungs show bilateral lung metastases. A needle biopsy is performed, and you are planning to review the specimen with the pathologist. Which of the following diagnoses are you suspecting?
   1. Pure fetal histology hepatoblastoma
   2. Embryonal sarcoma of the liver
   3. Fibrolamellar hepatocellular carcinoma
   4. Small cell undifferentiated hepatoblastoma
   5. Conventional hepatocellular carcinoma

**Answer: d (Small cell undifferentiated hepatoblastoma)**This is a typical presentation of a small cell undifferentiated hepatoblastoma: infant with a very aggressive primary liver tumor and low alfa-fetoprotein. Small cell undifferentiated hepatoblastomas share molecular alterations with rhabdoid tumors (*hSNF5* alterations), and on standard pathology they have absent INI staining. Pure fetal histology hepatoblastoma usually presents with localized disease and has an excellent prognosis. Fibrolamellar and conventional hepatocellular carcinomas, while also having a very aggressive clinical behavior, present in the second decade of life. Embryonal sarcoma of the liver is a less aggressive malignancy that usually presents after 3 years of age.

**Other Rare Tumors**

You have been asked to see a 15-year-old girl who is being referred for evaluation of an ovarian mass. Her history is also significant for secondary amenorrhea, and physical examination shows signs of virilization. As you review her family history, what syndrome will you consider?

* 1. Li-Fraumeni syndrome
  2. DICER-1 syndrome
  3. Turner syndrome
  4. Beckwith-Wiedemann syndrome
  5. Lynch syndrome

**Answer: b (DICER-1 syndrome)**

This girl has a virilizing ovarian mass, consistent with a testosterone-secreting stromal sex-cord tumor—either a Sertoli-Leydig cell tumor or a gynandroblastoma, which is extremely rare in children. Approximately 50% of patients with these tumors have a germline mutation of *DICER-1.* Other malignancies occurring in DICER-1 families include pleuropulmonary blastoma, cystic nephroma, Wilms’ tumor, medulloblastoma, ciliary body medulloepithelioma, and uterine cervix embryonal rhabdomyosarcoma.

A 4-month-old boy with family history of MEN2A syndrome on the paternal side has been referred to you for cancer screening. Which of the following markers will be useful in his management?

* 1. Alpha-fetoprotein
  2. Inhibin B
  3. Dehydroepiandrosterone
  4. Calcitonin
  5. Lactate dehydrogenase

**Answer: d (Calcitonin)**

Children with MEN2A and MEN2B syndrome are at a very high risk of developing medullary thyroid carcinoma. The *RET* mutations associated with MEN2B are very penetrant, and prophylactic thyroidectomy is recommended in the first months of life. For patients with MEN2A, a delayed prophylactic thyroidectomy is usually recommended, and in such cases, calcitonin can be a useful marker to guide timing of the surgery for those patients with moderate-risk *RET* mutations. Alpha-fetoprotein is a tumor marker for several embryonal malignancies, including hepatoblastoma, yolk sac tumor, and pancreatoblastoma. Inhibin B is a tumor marker for Sertoli-Leydig tumors, and dehydroepiandrosterone is usually elevated in childhood adrenocortical carcinoma.

You have been asked to see a 15-year-old Black male who presented with nasal obstruction and epistaxis and bilateral cervical lymphadenopathies. Physical examination and imaging studies show a large nasopharyngeal mass, and a biopsy of the mass shows undifferentiated carcinoma. As you complete the baseline workup, what viral studies should you consider?

* 1. Cytomegalovirus
  2. Hepatitis B virus
  3. Epstein-Barr virus
  4. Human immunodeficiency virus
  5. Human papilloma virus

**Answer: c (Epstein-Barr virus)**

This patient has a very typical presentation of nasopharyngeal carcinoma, which usually occurs in adolescents and with a higher incidence in patients who are Black. The most common histologic subtype of nasopharyngeal carcinoma in children is the undifferentiated, also called lymphoepithelioma, and it is almost universally associated with Epstein-Barr infection. The human papilloma virus is associated with squamous cell carcinomas of the head and neck in adults.