Liver: Hepatoblastoma

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Classification

There used to be multiple classification systems to distinguish between the different stages of hepatoblastoma development, making it difficult to compare results obtained by different study groups. In 1999 it was agreed that all groups would use the criteria of the SIOPEL group (SIOP = International Society of Paediatric Oncology). This group used (pre-treatment) intrahepatic tumor extension (PRETEXT) to classify the tumors. In this system the liver is divided into four sectors and the stages are based on the tumor extension within these four sectors:

- Stage I: tumor in one sector, three adjoining sectors free;
- Stage II: tumor involves two sectors, two adjoining sectors free;
- Stage III: tumor involves two or three sectors, one sector or two non-adjoining sectors free;
- Stage IV: tumor in all four sectors, no free sector.

Additional information is noted as follows:

- Hepatic vein (V): presence of hepatic vein involvement;
- Portal vein (P): presence of portal vein involvement;
- Extrahepatic (E): presence of extrahepatic direct spread, limited to enlargement of the hilar lymph nodes;
- Metastases (M): presence of distant metastases.

Etiology

Most cases of hepatoblastoma are sporadic, but sometimes it is found to be associated with Beckwith-Wiedemann syndrome (BWS) or familial adenomatous polyposis coli (FAP).

Epidemiology

Hepatoblastoma occurs with a world-wide incidence of 0.5-1.5 cases per million children. It accounts for between 60 and 85% of all hepatic tumors in children and therefore it represents the most common type of pediatric liver tumor.

Clinics

Because of missing clinical symptoms during early growth, patients often present with locally extended tumors. The right lobe is involved three times more commonly than the left. Bilobar involvement is seen in 20-30% of the cases, multicentric involvement in 15%. Distant metastases usually occur very late in advanced disease stages. Often these patients have elevated serum alpha-fetoprotein (AFP) levels. Although there is no clear correlation between AFP and outcome, AFP level is a sensitive marker of disease. Furthermore, there is a correlation between AFP and extent of disease, and the rate of decline in AFP with treatment is prognostic.

Pathology

Histologically, HB can be classified into two major types: epithelial (56% of the cases) and mixed epithelial/mesenchymal (44% of the cases). The presence of mesenchymal elements has been associated with an improved prognosis in patients with advanced disease. The epithelial type can be further subdivided into 4 subtypes: pure fetal (31%), embryonal (19%), macrotrabecular (3%) and small cell undifferentiated (3%). In completely resected tumors a pure fetal histology confers a better prognosis, whereas a small cell undifferentiated histology is associated with a poor prognosis.
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Cytogenetics

Cytogenetics Morphological

Although cytogenetic analyses of HBs have been far from numerous, certain characteristics can be deduced from the literature. The most recurrent cytogenetic abnormalities are the presence of extra copies of chromosomes 2q and 20. Four cases have been reported with a t(1;4)(q12;q34) resulting in partial trisomy 1q and partial monosomy 4q. Chromosome breaks occur frequently at 1q12-q21 and 2q35-q37. In order to obtain a global overview of chromosomal losses and gains, two comparative genomic hybridization studies were performed on a total of 30 HBs. The results showed frequent gains of chromosomes 1, 2, 7, 8, 17, 20 and 22q, and loss of 4q.

Genes involved and proteins

Note

Genes that play a causative role in the development of HB should be sought in the region associated with BWS (11p15.5). In addition, the FAP-genes APC and b-catenin represent good candidate genes for the onset of these tumors.

BWS, with which HB has been associated, has been linked to chromosome 11p15.5. In molecular analyses of sporadic HBs loss of heterozygosity (LOH) of this region has been found (33% of the cases in the largest series). This LOH has been shown to be uniquely of maternal origin, indicating a role for genomic imprinting in the disease. Indeed, loss of imprinting of insulin-like growth factor 2 (IGF2, located on 11p15.5) was found in a few cases. Loss of imprinting of the closely related H19 gene was found in one case but not in others.

Since HB also occurs with increased frequency in FAP patients, the APC gene has been the focus of some studies. Indeed, this gene shows a high frequency of loss of function mutations in sporadic HBs (69%). The APC gene has been implicated in the wingless/WNT developmental pathway, and another gene, b-catenin, that also plays a role in this pathway, has been shown to undergo activating mutations in a substantial amount of HBs.

In addition, mutations of p53 and LOH of chromosome 1 have been found.

References


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