Published in final edited form as:
Pediatr Blood Cancer. 2009 March ; 52(3): 312–313. doi:10.1002/pbc.21893.

SMARCB1/INI1 Alterations and Hepatoblastoma: Another Extrarenal Rhabdoid Tumor Revealed?

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Hepatoblastoma (HB) is the most common primary hepatic tumor of childhood. Ninety percent of cases present in the first 5 years and approximately 60% within the first 2 years of life [1]. The annual rate of incidence is approximately 1 case per 1,000,000 children in Western countries [2]. Sixty percent of tumors are classified as epithelial, and about 40% as mixed epithelial-mesenchymal, characterized by an admixture of osseous, cartilaginous and, more rarely, skeletal muscle elements [3]. Three main histologic subtypes of epithelial HBs are distinguished: *fetal*, *embryonal*, and *small cell undifferentiated* (initially described as anaplastic). The rare small cell undifferentiated pattern is usually observed during the first 6 months of life. Microscopically it consists of small, round, darkly staining cells resembling neuroblasts with little evidence of liver cell differentiation by H&E staining [4]. Small cell histology has been reported to have a high mortality even if the initial resection is complete [5]. The rare rhabdoid tumors of the liver, which can occur as a component of HB or in pure form, are aggressive tumors of young infants and carry a poor prognosis [5,6].

Recent molecular genetic studies of rhabdoid tumors of the kidney, soft tissues (RT) and central nervous system (the latter usually referred to as "atypical teratoid/rhabdoid tumors, AT/RT") have consistently revealed deletions and mutations of the *SMARCB1/INI1* gene located in chromosome band 22q11.2 [7,8]. Predisposing germline mutations, homozygous gene inactivation in tumors and an essential role in development in mouse models are all consistent with its role as a tumor suppressor gene. *SMARCB1/INI1* is a core member of the ATP-dependent SWI/SNF chromatin remodeling complex and thus functions in the activation and repression of a large variety of target genes [9]. The specific role in tumor initiation is still being defined.

The lack of nuclear staining for the SMARCB1/INI1 protein product by immunohistochemistry has proven a useful tool in the diagnosis of RTs and AT/RTs, with multiple studies confirming absence of detectable expression of the protein in rhabdoid tumor cell nuclei, but retention of expression in surrounding normal tissues and in most other tumor types tested [10,11]. These molecular and immunohistochemical features have also characterized rhabdoid tumors of the liver [12].

Rhabdoid cells that are morphologically identical to those seen in RTs have been identified as a component of other soft tissues sarcomas such as synovial sarcoma [13], leiomyosarcoma [14] and extraskeletal myxoid chondrosarcoma [15], as well as in renal [16], gastric [17] and other carcinomas where they appear to be associated with more aggressive behavior [18]. The rhabdoid component of these tumors may not, however, share the genetic and immunohistochemical features of RTs of childhood [19]. Conversely, the

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spectrum of tumors characterized by mutations in the *SMARCB1/INI1* gene has also been recently expanded beyond tumors with a rhabdoid histologic phenotype, to include hereditary schwannomas [20,21], extraskeletal myxoid chondrosarcomas [22], and pediatric undifferentiated sarcomas lacking rhabdoid features [23].

In this current issue of *Pediatric Blood & Cancer*, Trobaugh-Lotrario et al. confirm the adverse prognosis of the small cell undifferentiated variant of hepatoblastoma (SCU). A total of eight patients with molecular, cytogenetic or immunohistochemical evidence for inactivation of *SMARCB1/INI1* were identified in this review of forty cases, eleven of which were examined by the authors and a further 29 culled from the literature. Due to the fact that only a select number of cases had slides or tissue for study, it is not possible to estimate the percentage of SCU–HB patients that present these changes. As the authors point out, there are biologic and clinical similarities between the SCU–HB variant and extra-renal or renal rhabdoid tumors, including young age at onset, higher stage disease at presentation and a more aggressive clinical course.

All rhabdoid tumors, regardless of anatomic location, that have mutations and/or deletions of both copies of *SMARCB1/INI1*, demonstrate loss of protein expression as assessed by immunohistochemistry [10,11]. Tumors that demonstrate homozygous inactivation of this gene, regardless of age, stage or histology, are most likely to have rhabdoid tumors, and the patients should be treated aggressively. In contrast, however, it is not clear that loss of expression of the protein is sufficient to make a diagnosis of rhabdoid tumor, especially when only a portion of the cells show loss of staining, or the tumor cells demonstrate variable staining. It is formally possible that loss of SMARCB1/INI1 protein expression may be an indirect result of inactivation or increased expression of an upstream gene that regulates SMARCB1/INI1. The authors demonstrate variably retained positivity for SMARCB1/INI1 staining in SCU–HB, in cases in which SCU elements are found within an otherwise typical HB. Further, as the authors point out, rhabdoid cells and SCU elements may co-exist within the same tumor. At present, therefore, SCU–HB and rhabdoid tumors should not be considered identical entities. Molecular diagnosis for patients with suspected rhabdoid tumors or those tumors that demonstrate loss of expression of the protein, including SCU–HB, is important to identify those patients who require aggressive therapy. Moreover, it is critical to identify those patients who have germline deletions or mutations of SMARCB1/INI1. Affected individuals are more likely to develop multiple primary tumors, and unaffected carriers, including parents and siblings, are at increased risk of cancer. More extensive comparative clinico-pathologic and molecular genetic analyses will help to clarify differences between rhabdoid tumors and the subtypes of HB, which will be facilitated by combined biologic and therapeutic protocols for these rare but devastating diseases.

REFERENCES

1. Stocker JT. Hepatic tumors in children. Clin Liver Dis. 2001; 5:259–281. viii–ix. [PubMed: 11218918]
2. Schnater JM, Kohler SE, Lamers WH, et al. Where do we stand with hepatoblastoma? A review. Cancer. 2003; 98:668–678. [PubMed: 12910509]
3. Ishak, KG.; Goodman, ZD.; Stocker, JT. Tumors of the Liver and Intrahepatic Bile Ducts Third Series, Fascicle 31. Washington: Armed Forces Institute of Pathology; 2001.
4. Gonzalez-Crussi F. Undifferentiated small cell (“anaplastic”) hepatoblastoma. Pediatr Pathol. 1991; 11:155–161. [PubMed: 1849636]
5. Haas JE, Feusner JH, Finegold MJ. Small cell undifferentiated histology in hepatoblastoma may be unfavorable. Cancer. 2001; 92:3130–3134. [PubMed: 11753992]
6. Yuri T, Danbara N, Shikata N, et al. Malignant rhabdoid tumor of the liver: Case report and literature review. Pathol Int. 2004; 54:623–629. [PubMed: 15260854]

7. Biegel JA, Zhou JY, Rorke LB, et al. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res. 1999; 59:74–79. [PubMed: 9892189]
8. Versteege I, Sevenet N, Lange J, et al. Truncating mutations of hSNF5/INI1 in aggressive paediatric cancer. Nature. 1998; 394:203–206. [PubMed: 9671307]
9. Roberts CW, Orkin SH. The SWI/SNF complex–chromatin and cancer. Nat Rev Cancer. 2004; 4:133–142. [PubMed: 14964309]
10. Hoot AC, Russo P, Judkins AR, et al. Immunohistochemical analysis of hSNF5/INI1 distinguishes renal and extra-renal malignant rhabdoid tumors from other pediatric soft tissue tumors. Am J Surg Pathol. 2004; 28:1485–1491. [PubMed: 15489652]
11. Judkins AR, Mauger J, Ht A, et al. Immunohistochemical analysis of hSNF5/INI1 in pediatric CNS neoplasms. Am J Surg Pathol. 2004; 28:644–650. [PubMed: 15105654]
12. Wagner LM, Garrett JK, Ballard ET, et al. Malignant rhabdoid tumor mimicking hepatoblastoma: A case report and literature review. Pediatr Dev Pathol. 2007; 10:409–415. [PubMed: 17929989]
13. Oda Y, Hashimoto H, Tsuneyoshi M, et al. Survival in synovial sarcoma. A multivariate study of prognostic factors with special emphasis on the comparison between early death and long-term survival. Am J Surg Pathol. 1993; 17:35–44. [PubMed: 8383468]
14. Oda Y, Miyajima K, Kawaguchi K, et al. Pleomorphic leiomyosarcoma: Clinicopathologic and immunohistochemical study with special emphasis on its distinction from ordinary leiomyosarcoma and malignant fibrous histiocytoma. Am J Surg Pathol. 2001; 25:1030–1038. [PubMed: 11474287]
15. Oshiro Y, Shiratsuchi H, Tamiya S, et al. Extraskeletal Myxoid Chondrosarcoma with Rhabdoid Features, with Special Reference to Its Aggressive Behavior. Int J Surg Pathol. 2000; 8:145–152. [PubMed: 11493979]
16. Cheng JX, Tretiakova M, Gong C, et al. Renal medullary carcinoma: Rhabdoid features and the absence of INI1 expression as markers of aggressive behavior. Mod Pathol. 2008; 21:647–652. [PubMed: 18327209]
17. Kuroiwa K, Kinoshita Y, Shiratsuchi H. Renal cell carcinoma with rhabdoid features: An aggressive neoplasm. Histopathology. 2002; 41:538–548. [PubMed: 12460207]
18. Oda Y, Tsuneyoshi M. Extrarenal rhabdoid tumors of soft tissue: Clinicopathological and molecular genetic review and distinction from other soft-tissue sarcomas with rhabdoid features. Pathol Int. 2006; 56:287–295. [PubMed: 16704491]
19. Al-Hussaini M, Hirschowitz L, McCluggage WG. Uterine neoplasms composed of rhabdoid cells do not exhibit loss of INI1 immunoreactivity and are not related to childhood malignant rhabdoid tumor. Int J Gynecol Pathol. 2008; 27:236–242. [PubMed: 18317218]
20. Boyd C, Smith MJ, Kluwe L, et al. Alterations in the SMARCB1 (INI1) tumor suppressor gene in familial schwannomatosis. Clin Genet. 2008; 74:358–366. [PubMed: 18647326]
21. Patil S, Perry A, Maccollin M, et al. Immunohistochemical analysis supports a role for INI1/SMARCB1 in hereditary forms of schwannomas, but not in solitary, sporadic schwannomas. Brain Pathol. 2008; 18:517–519. [PubMed: 18422762]
22. Kohashi K, Oda Y, Yamamoto H, et al. SMARCB1/INI1 protein expression in round cell soft tissue sarcomas associated with chromosomal translocations involving EWS: A special reference to SMARCB1/INI1 negative variant extraskeletal myxoid chondrosarcoma. Am J Surg Pathol. 2008; 32:1168–1174. [PubMed: 18580682]
23. Kreiger PA, Judkins AR, Russo PA, et al. Loss of INI1 Expression Defines a Unique Subset of Pediatric Undifferentiated Soft Tissue Sarcomas. Mod Pathol. 2008 accepted.