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Small Cell Undifferentiated Variant of Hepatoblastoma: Adverse Clinical and Molecular Features Similar to Rhabdoid Tumors

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Abstract

Background—Small cell undifferentiated (SCU) histology in patients with stage I hepatoblastoma (HB) predicts an increased risk of relapse. We sought to determine the significance of SCU histology in patients with unresectable HB.

Procedure—Patients enrolled on the pediatric Intergroup (INT0098) trial for HB and patients from the personal consultation files of two of the authors (MF, LG) were reviewed for cases with SCU histology. These patients were compared with SCU HB patients identified by literature review.

Results—Eleven patients were studied. All patients with reported AFP results exhibited normal or minimally increased serum AFP levels. None of the patients survived: 10 died of disease progression, and 1 died from treatment complications. Immunostaining revealed that tumors from six of six patients tested were INI1 negative. Cytogenetic and molecular abnormalities in 1 patient (and 2 patients from the literature review) were similar to those described in rhabdoid tumors. Comparison with patients from the literature review revealed similar results except that four of 29 patients survived without evidence of disease.

Conclusions—SCU histology in HB patients is associated with an adverse outcome. These tumors appear to be biologically different from non-SCU HB. Evaluation of patient characteristics and outcomes for children with SCU HB and/or those with low AFP levels should be determined from large cooperative group studies. In the meantime, we suggest patients with unresectable HB containing SCU elements have careful cytogenetic, molecular, and immunohistochemical evaluation to ascertain rhabdoid features and receive treatment that differs from that provided for other HB patients.

Keywords

Hepatoblastoma; small cell; undifferentiated; rhabdoid; anaplastic

INTRODUCTION

Malignant tumors of the liver in children are most often hepatoblastoma (HB) or hepatocellular carcinoma. For infants and young children, hepatoblastoma is the predominant type of liver tumor. Though there has been progress made in treating children with hepatoblastoma, there are remaining problems: children with metastatic disease at diagnosis or whose AFP values drop slowly in response to therapy are examples [1,2]. Histologic evaluation in children with non-resectable HB is of uncertain significance because small biopsies may not be representative of these often highly diverse neoplasms. Pathologic classification varies from well-differentiated hepatocytes that resemble normal fetal liver cells to those that resemble normal embryonic liver cells to those that are small and totally undifferentiated [3]. The latter cells usually constitute a small proportion of a mixed fetal/embryonal HB (Figure 1A), but in infants they may constitute the entire malignancy.

Those with pure fetal histology and a low mitotic rate are curable without chemotherapy if localized and fully resected at diagnosis (COG stage I) [1,4,5,6]. We have previously reported an adverse effect of SCU histology on the prognosis of patients with stage I HB, especially when greater than 75% of tissue consisted of small cell elements [7]. To further examine this observation, we reviewed the files of patients enrolled on the most recently completed pediatric intergroup trial for HB, our personal consultation files, and the literature to determine the significance of SCU histology in HB patients whose tumors were unresectable at diagnosis.

METHODS

We reviewed records of patients in our personal consultation files (MF, LG) and those of children enrolled on the INT0098 study (CCG 8881 and POG 8945) for those with mention of SCU and/or low serum AFP at diagnosis. INT0098 was the most recently completed intergroup trial of HB at the time. All available records for the 182 evaluable patients on INT0098 were reviewed.

The medical literature was searched using PubMed and EMBASE from 1970 to 2007 for reports of children with SCU type of HB. All known final reports of clinical trials of HB conducted by the major pediatric cooperative groups were reviewed, as were abstracts from the American Society of Clinical Oncology and American Society of Pediatric Hematology and Oncology meetings over the past 10 years.

The small cell component of HB is illustrated in Figure 1A. These cells are undifferentiated in routine histologic preparations, have minimal cytoplasm and round lightly chromatic nuclei with inconspicuous nucleoli, fail to form tubules or to cohere, infiltrate the liver while sparing bile ducts, and often invade veins. When comprising a portion of an otherwise typical HB with epithelial and possibly mesodermal derivatives, they are identified as discrete small nests most often associated with embryonal elements. Immunohistochemically, they share with rhabdoid tumors biphenotypic expression of intermediate filaments typical of epithelial and mesenchymal cells, cytokeratin and vimentin, which facilitates their detection. INI1 antibody produces a variable degree of nuclear staining, unlike rhabdoid tumor cells, which are always negative.

Special studies were performed on all cases in the original review in which SCU foci were described. Tissue from one patient registered on COG/POG studies was analyzed by comparative genomic hybridization (CGH) array and sequence analysis for the *SMARCB1/INI1* gene. Staining for the presence of the INI1 protein was performed on all six patients' samples for which we had slides. See Supplemental Appendix for further methods details.

RESULTS

From the first part of our study, eleven patients with initially incompletely resected SCU HB were identified: 4 from review of the INT0098 database and 7 others from the consultation files. Demographics are shown in Table I. Patients were staged according to either the North American Intergroup method[1] or the PRETEXT system[8] used by SIOP investigators. Patients ranged in age from 3 to 16 months (median 8 months). The stage distribution was 0, 3, and 8 patients for stages II, III, and IV, respectively using the intergroup system. There were 10 males and 1 female. Six patients' serum AFP results were reported: 3 had results in the normal range, 2 had results only minimally elevated for age (95, 2891 ng/mL), and one patient's AFP was 12 ng/mL following resection. Immunostaining for INI1 conducted on six tumors (patients 3, 4, 7, 8, 9, 11) was negative. (Figure 1B). Whole genome comparative genomic hybridization of the INI1 gene locus in one patient (#3) revealed a homozygous deletion of 260 kb in the 22q12 region, which harbors the *SMARCB1/INI1* gene. This deletion was not detected by conventional cytogenetic methods (Figure 2).

The treatments these patients received varied, although most treatments included cisplatin and doxorubicin, with or without vincristine and 5-fluorouracil in some combination. Of the eleven patients studied, none survived. Ten patients died of disease. One patient died of sepsis.

Our literature review identified another 29 cases with initially incompletely resected SCU HB. Demographics are shown in Table 2 [9–22]. Patients ranged in age from 2 to 138 months (median 15 months). The stage distribution was 5, 9 and 3 patients for stages II, III, and IV, respectively in the intergroup system and 2, 7 and 3 patients for PRETEXT II, III and IV. There were 19 males and 10 females. Twenty-two patients' serum AFP results were reported: 10 had values in the normal range, 8 had values only minimally elevated for age (10.4–307 ng/mL), and 4 had results reported as markedly elevated. Twenty-three patients were described as anaplastic or SCU, and 6 patients had SCU histology in combination with embryonal and/or fetal histology. The reports did not include descriptions of the degree or percentage of SCU histology.

The treatments these patients received varied significantly. Of those reported, all but one patient received chemotherapy. Most treatments included cisplatin, doxorubicin, vincristine and 5-fluorouracil in some combination. Four patients underwent liver transplantation, two of whom are long term survivors.

Only 4 of these 29 patients are alive without evidence of disease at the time of the reports. Twenty-two patients died of disease, including one patient reported to have died of disease and treatment-related complications. One patient died of complications following liver transplantation, and one patient died of a surgery-related death. One patient was lost to follow up after developing recurrent disease (#14).

The 4 patients alive without evidence of disease were older at diagnosis (ages 27.6 months, 28 months, 5 years and 11 years). In addition, two of the three with AFP data had levels said to be markedly elevated at diagnosis. Both of these features are distinctly atypical compared to other patients in this review. We were unable to obtain slides on these cases to independently confirm their stated histology. One of these patients was reported to have a combination of embryonal and anaplastic histology, and the remaining three had anaplastic features. Three were stage III and one was PRETEXT stage II. Two of the survivors underwent liver transplantation after chemotherapy. The agents used prior to transplant were not identified.

Cytogenetic and molecular results included three patients (3, 15, 19) who had tumor tissue translocations involving chromosome 22 at band 11q: t(10;22)(q26;q11) in two and t(22;22)(q11;q13) in one. As a group, the patients with confirmed genetic alterations and/or INI1 negative immunostaining (patients 3, 4, 7, 8, 9, 11, 15, 19) were young (3 to 15 months at diagnosis, median 7.5 months), advanced in stage (II in 1, III in 2, and IV in 5) and lacked elevation in serum AFP at diagnosis in 3 of the 4 reported. All patients died: 7 of disease and 1 of sepsis.

DISCUSSION

SCU histology in HB patients is associated with an adverse outcome [3,7]. Even a small proportion of SCU histology may confer this apparent disadvantage on patients with Stage I disease [7]. Only 4 of 40 patients we identified with mention of this histology were alive without evidence of disease 5 to 70 months following diagnosis, and none of the eleven patients whose slides the authors reviewed survived. In general, these eleven patients were younger, presented with higher stage disease, and were more likely to exhibit INI1 gene abnormalities, similar to patients with rhabdoid tumors.

The stage distribution for patients with SCU histology is not significantly different from patients with other histologic types of HB. However, the SCU HB patients with confirmed genetic alterations and/or INI1 negative immunostaining (patients 3, 4, 7, 8, 9, 11, 15, 19) more often presented with advanced stage compared with patients with other histologic types of HB (12.5% stage II, 25% stage III and 62.5% stage IV compared with 5% stage II, 64% stage III and 31% stage IV on CCG 8881 [1]). The male predominance of patients with SCU HB in our study is slightly more pronounced than in hepatoblastoma overall: 73% (29 of 40 patients) compared with 62% male (113 of 182 patients) on CCG 8881 [1]. In the group of SCU HB patients with INI1 alterations and/or negative immunostaining, this slight increase in male gender is similar (75% male) to the male predominance in our study. Though they had poorer outcomes than patients with Stage I HB without SCU histology, the patients with SCU histology and Stage I disease fared better than those with Stage II to IV SCU HB in our study. Of the 16 patients with Stage I SCU HB reported by Haas et al, 6 patients survived event-free, 5 patients survived following recurrence, and 5 patients died of recurrent disease [7].

As is the case for all HB histologic types, aggressive attempts for full surgical resection is essential for cure, and patients in whom a full resection appears to be problematic should be referred early to centers with expertise with liver transplantation in HB patients. Extent of surgical resection was reported for 34 of the 40 patients in the overall cohort examined, although margin status and/or gross tumor spillage was explicitly stated in only 9 patients. Of the 34 patients, 14 did not undergo a resection (one due to parental refusal; otherwise details were not reported). These 14 patients all died of progressive disease. All 4 patients who survived had a complete resection. Two of these four survivors had complete resection in conjunction with liver transplantation. These 2 patients received chemotherapy before and after transplant. One of the 4 surviving patients had a complete resection with negative margins after 3 cycles of cisplatin and doxorubicin, and the fourth surviving patient had a complete resection after 4 months of vincristine and cyclophosphamide. No margin status was reported. The patients who underwent liver transplantation tended to fare better, but this occurred for only four of the patients in this series. Earlier attempts at full resection may be more critical for patients with SCU histology, given the poor response of these tumors to the standard chemotherapy used for HB.

In the complete cohort of patients reported here, AFP levels were normal or only mildly increased in 24 of the 28 patients with data. Patients with low or negative AFP have been

reported to fare worse than those with elevated AFP levels [23]. More extensive pathologic review of the entire tumor of these patients with non-elevated AFP may reveal areas of SCU histology, because small biopsies at diagnosis may easily miss one component of a large heterogeneous tumor (Figure 1A).

Some of these tumors may be more appropriately classified as rhabdoid or rhabdoid-like tumors. Immunostaining for INI1 was negative for six patients (as would be expected in rhabdoid tumors), and it is known that rhabdoid tumor of the liver has been initially misdiagnosed as HB [24]. Both tumors share the simultaneous expression of intermediate filaments typical of epithelial and mesenchymal cells, cytokeratin and vimentin. Some of the clinical and biologic factors of both HB and rhabdoid tumors are also similar, but not identical (e.g., gender and proportion metastatic at diagnosis). It is difficult to classify the tumors as rhabdoid tumors definitively given the occasional INI1 positivity in some of the SCU, especially in the setting of an otherwise typical HB.

When SCU elements are found within otherwise typical HBs having fetal and embryonal histology, immunostaining for INI1 varies, with some nuclei positive, in contrast to cells with rhabdoid features. When otherwise indistinguishable small undifferentiated cells form the entirety of a neoplasm, it typically occurs in infancy, has negative nuclear staining for INI1, fails to secrete alpha-fetoprotein, and behaves like the rhabdoid tumor. Both cell types display biphenotypic expression of the intermediate filaments, cytokeratin and vimentin, but in the rhabdoid cell those filaments are more abundant and in routine stains are larger with eosinophilic cytoplasm, an eccentric nucleus and prominent nucleolus. On rare occasions, the two morphologically distinct cell types may be found within the same neoplasm. A thorough comparative molecular genetic analysis will provide ultimate clarification of the similarities and differences between these cell types. We are using laser capture microdissection to isolate the various cell types for this specific purpose.

Cytogenetic and molecular studies on the tumors of 4 patients in our report revealed translocations or deletion of the 11 q band on chromosome 22. Rhabdoid tumors are associated with cytogenetic abnormalities involving chromosome 22 [25–28]. Compared with other SCU HBs, tumors with cytogenetic, molecular and clinical characteristics of rhabdoid tumors should be differentiated from HB and treated like rhabdoid tumors. Although non-resected rhabdoid tumors have heretofore fared poorly, 5 patients with metastatic rhabdoid tumors of the kidney or liver have been treated successfully with ifosfamide, carboplatin and etoposide alternating with vincristine, doxorubicin and cyclophosphamide [29–32]. Patients with malignant rhabdoid tumors of the liver have also responded to other treatment regimens [33–34].

Further evaluation of patient characteristics and outcomes of HB patients with SCU histology should be reported by all the large pediatric cooperative groups. In the meantime, we suggest that HB patients with incompletely resected tumors containing SCU elements have careful cytogenetic, molecular and immunohistochemical evaluation to ascertain rhabdoid features and receive treatment that is more aggressive than provided for other HB patients. If SCU HB is indeed similar biologically to rhabdoid tumors, patients with SCU tumors of the liver should be included in future trials for rhabdoid tumors of other sites.

Drawbacks to this review are its retrospective nature, lack of thorough and expert pathology review on many of the cases to verify the presence and estimate the extent of the SCU component, and lack of clinical and surgical details in many cases. In addition, there may be a bias in that patients with small amounts of SCU histology not recognized in their tumors would not be reported as SCU HB. Nevertheless, this report constitutes by far the largest

series of patients with SCU HB reported to date, and provides important clues as to the molecular pathogenesis of at least some of these tumors.

Taken together, our results suggest that at least some SCU HB cases may actually represent a form of rhabdoid tumors. In order to improve treatment outcomes for all patients in this SCU class, we need a better understanding of their biology, further review of effect on outcome of earlier surgical resection with/without transplantation and a more specific therapy that targets the pathologic processes involved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
A. SCU foci in a hepatoblastoma with mixed histology (hematoxylin-eosin x250). B. INI1 immunohistochemistry: the bile duct epithelium (arrow) displays positive nuclear staining while it is negative in the small cells (x250).

Comparative genomic hybridization (CGH) array of tumor tissue from a six month old with hepatoblastoma of small cell undifferentiated histology. Tumor tissue is hybridized to normal lymphocyte DNA from the same patient. A. Schema of chromosome 22 at left indicates genomic regions analyzed. Plotted data indicated ratio of tumor to normal DNA. A ratio of 0 indicates no difference in copy number between tumor and normal DNA (indicated by black dots). Dots shown in green indicate regions of net loss of DNA copy number. The region indicated by red bracket indicates area with loss of two copies of chromosomal material. B. An expanded version of bracketed region, ranging from chromosomal position 22.32 to 22.58 M shows that the *SMARCB1/INI1* gene located at 22.44–22.50 MB, lies within the region of homozygous deletion.

Table 1

Patient characteristics.

Pt	Age at diagnosis	Sex	Stage	AFP (ng/mL)	Treatment	Resection	Response	Outcome	Ref.
1	16 months	M	IV	6	CSV	Not resected	Progressive disease	DOD	INT0098
2	10 months	M	III	12 (post-op)	CD	Gross total resection, positive margins, gross tumor spillage	Recurrent disease	DOD	INT0098
3	8 months	M	III	1	CD	Gross total resection, unclear margins, gross tumor spillage	Progressive disease	DOD	INT0098
4	3 months	M	IV	2891	CD	Not resected	Progressive disease	DOD	INT0098
5	12 months	M	III	WNL	CD, carboplatin	Not resected	Progressive disease	DOD	MF, LG
6	8 months	M	IV	95	C5VD	Not resected	Progressive disease	DOD	MF
7	9 months	M	IV	NR	NR	NR	Progressive disease	DOD 3 months from diagnosis	MF
8	7 months	F	IV	NR	C5VD, Ifosfamide	NR	NR	DOD 8 months from diagnosis	MF
9	8 months	M	IV	NR	NR	NR	NR	DOD	MF
10	7 months	M	IV	NR	NR	NR	NR	DOD	MF
11	3 months	M	IV	NR	NR	NR	NR	Died of sepsis	MF

Pt, patient; AFP, alpha-fetoprotein level; Ref., reference; M, male; C, cisplatin; 5, 5-fluorouracil; V, vincristine; DOD, died of disease; Finegold, patients from consultation files M Finegold; Gore, patient from consultation file of L Gore; Haas, patients from consultation files J Haas; INT0098, patients identified from review of intergroup trial files (includes CCG 8881 and POG 8549); D, doxorubicin; MF (INT0098), patients from Finegold files and also on INT0098; WNL, normal; POG, Pediatric Oncology Group; NR, not reported; F, female.

Table II

Cases from the Literature

Pt	Age at diagnosis	Sex	N.A. Stage	Pretext Stage	AFP (ng/mL)	Treatment	Resection	Response	Outcome	Ref.
12	2 years	M	III		WNL	CSVD, Bleo, CTX (3 cycles)	Unresectable	Progressive disease	DOD	9
13	15 months	F	IV		0	5VD, CTX (2 cycles), lung RT	Unresectable	Progressive disease	DOD	9
14	"Infant"	M	II		WNL	CSVD	Trisemen-tectomy at diagnosis	Recurrent disease at "a few months"	Not reported	10
15	7 months	M	II		WNL	CD (3 cycles)	Complete resection at diagnosis, unclear margins	Recurrent disease at 2 months post chemotherapy	DOD at 5 months from diagnosis	11
16	8 months	F	III		NR	CD (3 cycles)	Not resected	Progressive disease	DOD	12
17	8 months	F	IV		NR	VA	Left lobectomy	Recurrent disease at 2 months	DOD	12
18	5 years	M	IV		NR	Chemotherapy	Not reported	Progressive disease at 2 years	DOD at 2 years from diagnosis	13
19	15 months	F	III		WNL	CVD, ifosfamide, followed by liver transplant	Resection, margin with gross tumor infiltrates	Recurrent disease at 2 months post transplant	DOD at 2 months post transplant	14
20	28 months	M		II	NR	CD (3 cycles pre-operative)	Complete resection with negative margins	CR	Alive, NED (20 months)	15
21	24 months	M		III	NR	CD (3 cycles pre-operative)	Complete resection with negative margins	Recurrent disease at 3 months post surgery	DOD and therapy at 8 months post surgery	15
22	38 months	M		IV	NR	CD (3 cycles pre-operative)	Right trisemen-tectomy, negative margins	Recurrent disease at 2 months post surgery	DOD 6 months post surgery	15
23	5 years	F	III		85	CD (4 cycles)	Parents refused surgery	Initial response, then progressive disease	DOD 3 months post chemotherapy	16
24	11 years	F	III		WNL	V, CTX (X "4 months") pre-operative	Complete resection	CR	Alive, NED (19 months)	17
25	2 months	M	II		WNL	CSVD, RT	Right hepatic lobectomy at diagnosis	Recurrent disease at 2 months post surgery	DOD 5 months from diagnosis	18
26	5 months	M	II		307	CSVD, Bleo, CTX	Resection at diagnosis	Recurrent disease at 6 weeks post surgery	DOD 4.5 months from diagnosis	19

Pt	Age at diagnosis	Sex	N.A. Stage	Pretext Stage	AFP (ng/mL)	Treatment	Resection	Response	Outcome	Ref.
27	10 months	M	II		NR	5VD, CTX	Left hepatectomy at diagnosis with tumor spillage	Recurrent disease at 2 months post surgery	DOD 4 months from diagnosis	20
28	6 months	M	III		ME	No chemotherapy	Complete resection, liver transplant	CR	Died, hepatic artery thrombosis (4 months)	21
29	5 years	M	III		ME	Chemotherapy pre-transplant	Complete resection, liver transplant	CR	Alive, NED (43 months)	21
30	2 years	F	III		ME	Chemotherapy pre-transplant	Resected, liver transplant, vascular invasion and lymph node involvement	Recurrent disease	DOD at 35 days post transplant	21
31	2.3 years	M	III		ME	Chemotherapy pre-and post-transplant	Complete resection, liver transplant	Recurrent disease (pulmonary) at 7 months—resected	Alive, NED (70 months)	21
32	32 months	F		III	10.4	Carboplatin, CD	Not resected	Progressive disease	DOD 4.4 months	22
33	88 months	M		III	0.8	Carboplatin, CD	Microscopic residual	Partial response	Surgery-related death 7 months	22
34	12 months	M		IV	19.5	Carboplatin, CD	Not resected	Progressive disease	DOD at 2 months	22
35	7 months	M		III	14	CD	Not resected	Progressive disease	DOD at 4.5 months	22
36	10 months	F		II	30	Carboplatin, CD	Complete excision	Progressive disease	DOD at 4.2 months	22
37	14 months	M		III	8	Carboplatin, CD	Not resected	Progressive disease	DOD at 2.1 months	22
38	138 months	M		III	12	Carboplatin, CD	Not resected	Progressive disease	DOD at 2.8 months	22
39	6 months	M		IV	17	Carboplatin, CD	Not resected	Progressive disease	DOD at 0.5 months	22
40	130 months	F		III	1	Carboplatin, CD	Microscopic residual	Partial response	DOD at 13 months	22

Pt, patient; NA, North American; AFP, alpha-fetoprotein level; Ref., reference; M, male; WNL, normal; C, cisplatin; 5, 5-fluorouracil; V, vincristine; D, doxorubicin; Bleo, bleomycin; CTX, cyclophosphamide; DOD, died of disease; F, female; RT, radiation therapy; NR, not reported; A, actinomycin; CR, complete response; NED, no evidence of disease; ME, markedly elevated