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Rhabdoid tumor of the liver: Report of 6 pediatric cases treated at a single institute

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ABSTRACT

Background: Rhabdoid tumors (RTs) of the liver are rare, aggressive and nonsecreting malignancies occurring mainly during the first year of life. Definition of RT relies on characteristic morphology and on the inactivation of the SMARCB1 tumor suppressor gene. The aim of this study was to analyze clinical data, treatments and outcomes in our patients.
Patients and methods: 6 cases of patients treated in our institution for RT of the liver between January 2007 and January 2015 are reported. Variables examined included age at diagnosis, tumor stage, treatment and long-term survival.
Results: Median age at diagnosis was 5 months (range: 4–23). Normal for age serum AFP levels was observed in all patients. No patient presented with metastasis at diagnosis. The diagnosis of RT based on the loss of SMARCB1 was made early in 4 patients. The 2 others were initially diagnosed as nonsecreting hepatoblastomas. Median follow-up was 6 years (range: 2–9). All patients received chemotherapy, with variable regimens depending on initial diagnosis, followed by surgical resection. Three patients (50%) died of disease. Two of them were mistaken for nonsecreting hepatoblastomas at diagnosis and had recurrence shortly after completion of treatment. The third one presented a cardiac right atrium thrombus. Three patients (50%) are long-term survivors; they received multimodal therapy including chemotherapy according to protocol EpSSG NRSTS consisting of doxorubicin and surgical removal of the tumor performed within 3 months after diagnosis. One patient had adjuvant radiotherapy.
Conclusion: According to our results, search of SMARCB1 mutation or alternatively immunohistochemical assay for SMARCB1 in nonsecreting hepatoblastomas is mandatory to exclude RT. Chemotherapy according to EpSSG NRSTS protocol together with a surgical treatment seems justified to improve long-term survival.
Type of study: Retrospective study.
Level of evidence: Level IV.

Rhabdoid tumors (RTs) are aggressive, rare tumors of infancy, with an overall 5 year survival rate of approximately 30%, all stages considered. The annual age-standardized incidence reported in the literature is 0.6 per 1 million children; the incidence is higher during the first year of life (5 per 1 million children). RT can occur anywhere in the body, with the liver being the fourth most common site after the kidneys, brain and soft tissues [1].

RTs were first described in 1978, in the kidneys. The term rhabdoid was introduced initially because of the tumor cells' close histological resemblance to rhabdomyoblasts. To date, the exact cell type of derivation remains unknown, but the term of 'rhabdoid' continues to be used.

Definition relies on the biallelic inactivation of the SMARCB1 (SNF5/INI1/BAF47) tumor suppressor gene [2] and on a characteristic histological morphology. SMARCB1 is for SWI/SNF-related, matrix associated, actin-dependent regulator of chromatin subfamily B member 1, according to the Human Genome Organization. This gene is also named SNF5, INI1 or BAF47. SMARCB1 is a tumor suppressor gene located on

Abbreviation: AFP, alpha fetoprotein; CT, computed tomography; EpSSG NRSTS, European Pediatric Soft Tissue Sarcoma Study Group–Non Rhabdomyosarcoma Soft Tissue Sarcomas; HR, hazard ratio; MRI, magnetic resonance imaging; NWTS, National Wilms Tumor Study; PRETEXT, PRE-Treatment EXTent of disease; RT, rhabdoid tumor; SEER, Surveillance Epidemiology and End Results Program; SIOPEL, Société Internationale d'Ongologie Pédiatrique–Epithelial Liver Tumor Group; SMARCB 1, SWI/SNF-related matrix associated actin dependent regulator of chromatin subfamily B member 1.

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chromosome 22q11.2. Positional cloning identified the biallelic inactivation of SMARCB1 as the main oncogenic event in RT formation [3]. The main function of this complex is to control chromatin compaction and hence gene expression. The inactivation of SMARCB1 in early progenitors or stem cells might maintain progenitors or embryonic stem cells in an undifferentiated state, and therefore affect the expression of a large number of other oncogenes and tumor suppressor genes.

The association of mutation of SMARCB1, morphological characteristic and cytogenic features constitutes the diagnosis of RT. Rhabdoid cytomorphology is characterized by large, polygonal cells with eccentrically placed vesicular nuclei, prominent nucleoli, and an intracytoplasmic eosinophilic inclusion corresponding to aggregates of intermediate filaments.

Inactivation of both copies of the SMARCB1 gene leads to loss of protein expression in the nucleus, which can be detected by an SMARCB1 immunohistochemistry assay. Immunohistochemistry with anti-SMARCB1 (anti-INI1 or anti-hSNF5) is a very useful diagnostic tool [4].

Because of the rarity of the disease, there are only very few data available.

The aim of this study was to analyze clinical data, treatments and outcomes in our patients who present rhabdoid tumor of the liver.

1. Patients and methods

To be included in this study, all patients had to have been operated on for rhabdoid tumor of the liver at our institution, Department of Pediatric Surgery, Bicêtre Hospital (France), between January 2007 and January 2015, and had to have documented loss of SMARCB1 expression in the tumor by immunohistochemistry.

Study variables included: age at diagnosis, gender, tumor's dimension and localization at diagnosis, tumor stage, α fetoprotein (AFP), treatment modalities and long-term survival. Treatment modalities included: name of the cytotoxic agent, time of surgery, surgical resection margins, and radiotherapy. Responses were evaluated by ultrasonography, CT-scan and MRI. Complete remission was defined as no evidence of tumor on imaging. Disease progression was defined by increase of the tumor size on any imaging modality. Overall survival was defined as the interval between diagnosis and date of death or last follow-up.

2. Results

Between January 2007 and January 2015, a total of 90 patients underwent surgery for a malignant liver tumor at our institution, Bicêtre Hospital, with a specialized unit for pediatric hepatobiliary surgery and liver transplantation. Six patients presented with a rhabdoid tumor of the liver. Therapeutic strategy was done for all of them at our institution except for one case, which was referred to our hospital for surgery only.

Clinical information is summarized in Table 1. The median age at diagnosis was 5 months (range 2.5–23 months). There were 3 males and 3 females. Presenting symptoms were abdominal distension in four patients and fever in two patients. In all cases, abdominal contrast-enhanced computed tomography (CT) showed a large, unifocal parenchymal lesion. The lesion was heterogeneous with evidence of cystic components, represented by hypodense areas on contrast-enhanced CT and hyper-signal areas on T2 weighted images on MRI (Fig. 1).

Normal for age serum AFP levels were observed in all patients (median AFP = 89 ng/ml, range 10–379 ng/ml).

Five patients had a percutaneous hepatic biopsy and one a laparoscopic biopsy. For two patients the diagnosis of RT was made retrospectively after surgery, in our reference center (Department Of Pathology, Bicêtre Hospital); one, which was initially diagnosed as a small cell undifferentiated hepatoblastoma, and the other as a macrotrabecular hepatoblastoma. For two other patients, the initial histological diagnosis was a mixed hepatoblastoma, and the diagnosis was changed when SMARCB1 immunohistochemistry was done during centralized review. In the last two patients, the diagnosis of rhabdoid tumor was made at initial presentation based on the loss of SMARCB1 expression.

No germline mutations had been found in five patients. Data are not available for one patient. In four tumors, a homozygous deletion in SMARCB1 gene has been found.

No patient presented metastasis at the time of diagnosis. One patient presented with a liver tumor extension, as tumoral thrombus, within the inferior vena cava and the right cardiac atrium.

All patients received chemotherapy before surgery. Chemotherapy was variable depending on the initial diagnosis. Two patients were treated as nonsecreting hepatoblastoma, and received chemotherapy according to SIOPEL 4 protocol, a dose-dense cisplatin based chemotherapy. For these two patients, the tumor progressed on chemotherapy. Two other patients were initially treated as hepatoblastoma (before the result of SMARCB1 mutation) and then by chemotherapy for soft tissue sarcomas, according the European Pediatric Soft Tissue Sarcoma Study Group protocol for localized Non-Rhabdomyosarcoma Soft Tissue Sarcoma (EpSSG NRSTS protocol), containing vincristine, cyclophosphamide, doxorubicin, carboplatin and etoposide [5]. The two remaining patients received from the start, the chemotherapy for RT according the EpSSG NRSTS protocol.

A total of four patients received chemotherapy based on EpSSG NRSTS protocol. Three of them responded to chemotherapy (Fig. 2). In the fourth patient, the size of the hepatic lesion decreased but the thrombus extended further.

All children underwent surgery. The median time to surgery was 3.25 months (range 2–8 months). The resection was complete (R0) in 3 cases; 2 patients had microscopic positive resection margins (R1); and in the case of the patient with the cavoatrial tumor thrombus, despite the procedure being done by laparotomy and sternotomy with an atriotomy under cardiopulmonary bypass, the thrombus fell apart during surgery.

Postoperative chemotherapy contained vincristine, doxorubicin, cyclophosphamide, etoposide and ifosfamide according to EpSSG NRSTS protocol.

One patient received radiotherapy to the liver edge because of microscopic positive resection margins, and survived.

Table 1
Patient characteristics.

Pt.	Age (months)	Sex	AFP (ng/mL)	Diagnostic biopsy	Secondary histological review	Tumoral stage	Initial tumor length (mm)	Localization (liver segments involved)	PRETEXT
1	4	F	274	Small cell undifferentiated HB	SMARCB1 −	M0	105 × 104 × 62	2.3	1
2	6	M	34	Mixed HB, and soon after SMARCB1 −	SMARCB1 −	M0	87 × 69 × 96	4, 5, 6, 7, 8	3
3	23	F	<10	Macrotrabecular HB	SMARCB1 −	M0	72 × 65 × 70	4, 5, 6	3
4	7	M	379	SMARCB1 −	SMARCB1 −	M0	100 × 78 × 99	4, 7, 8	3
5	4	F	144	Mixed HB, and soon after SMARCB1 −	SMARCB1 −	M0	125 × 76 × 122	4, 5, 8	3
6	2.5	M	<10	SMARCB1 −	SMARCB1 −	M0, thrombus inferior vena cava	93 × 80 × 64	2, 3, 4	2