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Extra-Renal Rhabdoid Tumor: A Rare Malignant Tumor in Child about Four Cases

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Abstract

The rhabdoid tumor is a rare and aggressive tumor of pediatric population. Their grouping within a single entity is recent, following the discovery of a bi-allelic inactivation of the HSNF5/INI1 tumor suppressor gene in tumor cells. The present study aims to highlight the different epidemiological, clinical, histopathological, and immunohistochemical, and genetic features of extra-renal rhabdoid tumors in children. We present a case series of extra-renal rhabdoid tumor (ERRT), recorded at the Department of Pathology of University Hospital Center of Hassan 2 of Fez, in Morocco. From 2014 to 2022, four cases of extra renal rhabdoid tumor have been recorded in our department, their ages ranged from 2 to 7 months, and they were all boys. The sites most affected were the soft tissues. The histological analysis of all patients' specimens demonstrates the presence of rhabdoid cells. In the immunohistochemistry study, we noted a complete loss of INI-1 staining by tumor cells. However, the tumor cells have cytoplasmic positivity with a dot-like pattern for epithelial membrane antigen (EMA), CK AE1/AE3, and vimentin. Two of our patients were treated with chemotherapy, and 2 patients underwent surgery and then chemotherapy. The evolution was lethal in all cases. Rhabdoid tumor is a rare and aggressive tumor that occurs in children. It should be included in the differential diagnosis of rounds cells tumors of children and thought about in front of any aggressive isolated tumor. It is a challenging diagnosis for pathologists, especially with tiny biopsy material, or minor rhabdoid components.

Subject Areas

Pathology

Keywords

Rhabdoid Tumor, Extra-Renal, Immunohistochemistry, INI-1, SMARCB-1, Child, Diagnosis, Case Series

1. Introduction

The rhabdoid tumor (RT) is a rare and aggressive tumor in the pediatric population. It is characterized by a clinical polymorphism because of the different locations that they can affect [1]. Extrarenal rhabdoid tumor is rare, and it is most often confined to infants and children. Among fetal and neonatal rhabdoid tumors, the extrarenal rhabdoid tumor is more common than those in the kidney or brain [2]. A few cases of primary rhabdoid tumor occurring in extra-renal sites have been reported, particularly in the soft tissues [3]. Rhabdoid tumor was first identified, in 1978, by Beckwith and Palmer in the kidney as a sarcomatous variant of Wilms tumor [4]. Then, in 1981, Haas *et al.* classified it as a distinct histopathologic entity of kidney tumors [5].

Their grouping within a single entity is recent, following the discovery of a bi-allelic inactivation of the tumor suppressor gene SMARCB1 (hSNF5, BAF47, INI1), revealed by a complete loss of nuclear staining of INI-1 [6]. So, the histomorphological characteristics of rhabdoid tumors, their immunoreactivity to epithelial markers and vimentin, and the INI-1 loss are important tools for diagnosis. Therapeutic management remains multidisciplinary in the absence of any pre-established consensus. The present study aims to highlight the different epidemiological, clinical, histopathological, immunohistochemical, and genetic features of extra-renal rhabdoid tumors in children.

2. Methods

2.1. Patients Selection

This is a case series that was performed among four children with extra renal rhabdoid tumor, which was diagnosed at the department of Pathology of University Hospital Center of Hassan 2 of Fez in Morocco. Clinicopathological data were collected from patients' request forms and the pathology department files. From 2014 to 2022, four cases of extra renal rhabdoid tumor have been recorded in our department; details of clinical observations are summarized in **Table 1**.

2.2. Histopathological Analysis

The histological analysis has been performed on formalin-fixed and paraffin-embedded tissue sections, with hematoxylin-eosin-saffron staining.

Table 1. Clinicopathologic characteristics of our patients.

	Case 1	Case 2	Case 3	Case 4
Age (month)	2	4	7	2
Gender	Boy	Boy	Boy	Boy
Region	Head and neck (soft tissue)	Trunk (soft tissue)	Central nervous system (CNS)	Orbit (soft tissue)
Site	Forehead	Axillary	Vermis	Intra conical, retro-orbital
Pathological specimens	Excisional biopsy	Fine-needle aspiration then a biopsy	Surgical excision	Biopsy
Treatment	Surgery + chemotherapy	Chemotherapy	Surgery + chemotherapy	Chemotherapy
Evolution	Obstruction of the contralateral eye and nose	Lung and lymph nodes metastasis	Quadriventricular hydrocephalus	Local progression
Prognosis	Death	Death	Death	Death

2.3. Immunohistochemical Analysis

Immunohistochemical analysis was performed on a 4 µm tissue section from formalin-fixed and paraffin-embedded blocks, using primary antibodies according to the manufacturer's guidelines, with immunohistochemical stainers (Ventana Ventana BenchMark ULTRA). For all antibodies, positive and negative controls were performed, including the processing of normal tissue or tumor sections known to be positive. We have used the primary antibodies represented in Table 2.

3. Results

In the following, we are going to present the clinical, radiological and pathological details of each of our patients.

3.1. Case 1

A 2-month-old boy was referred to the pediatric department with a rapidly expanding soft tissue mass on the frontal region; it was present at birth, increasing progressively in volume. The clinical examination revealed a conscious child with a frontal mass of 6 cm (Figure 1(a)). Computerized tomographic imaging objectified a lobed cutaneous and subcutaneous tissue formation on the right front, taking the product of contrast heterogeneously without bone involvement, suggesting firstly hemangioma (Figure 2(a)). The systemic evaluation showed no metastatic disease. The child underwent an excisional biopsy of the lesion with frozen section analysis which was performed, coming back from a round cell tumor. Histological assessment of the resected specimen after fixation in formol 10%, showed skin tissue presenting in the dermis a round cell proliferation organized in sheets or nests separated by a fine capillary network and sometimes adopting an epithelial appearance (Figure 3(a)). The cells are medium to

Figure 1. Clinical finging: (a) Polylobed and hemorrhagic frontal mass of 6 cm. (b) Huge mass under the left clavicular, extending to the axillary region.

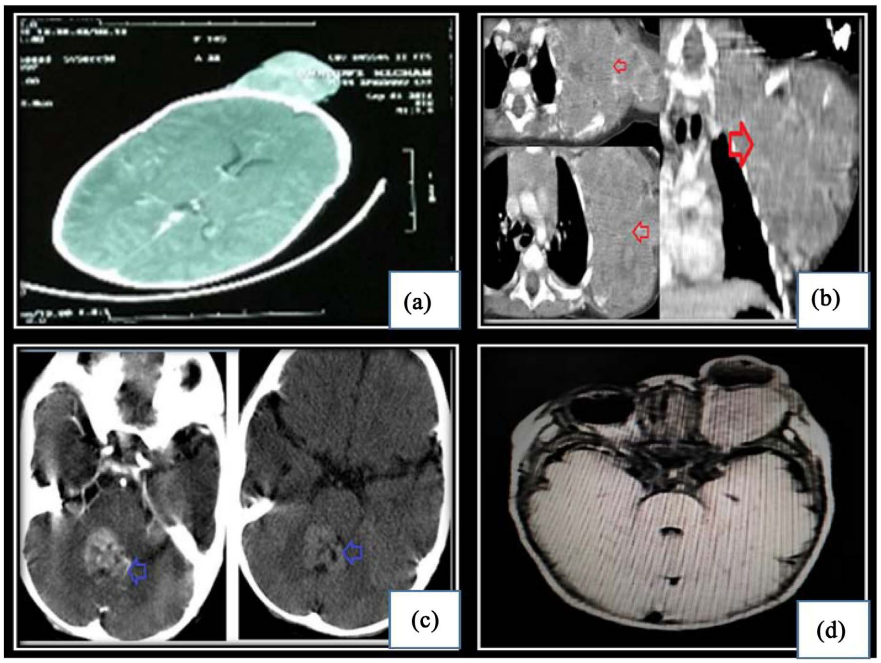

Figure 2. Computed tomography imaging: (a) Subcutaneous tissue lesion, polylobed with calcifications, without bone involvement. (b) Bulky left axillary mass, lobulated, heterogeneous, extending to the cervical region (red arrow). (c) Vermian tissue lesion, spontaneously dense, heterogeneously enhanced, extended to the right cerebellar hemisphere (blue arrow). (d) Left intra-conical retro-orbital tumor process responsible for proptosis.

Table 2. Details of antibodies used in our study.

Antibody	Clone	Staining
IN-1	BAF47/SNF5/25	Nuclear
Vimentin	V9	Cytoplasmic
CK	AE1/AE3	Cytoplasmic dot like
EMA	E29	Dot-like
Myogenin	LO26	Nuclear

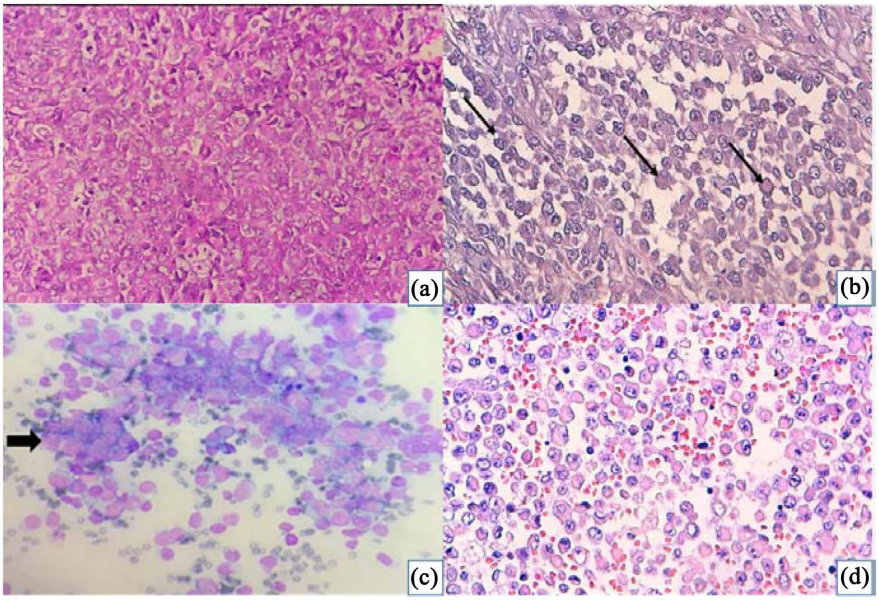

Figure 3. Histological finding: (a) Round cell proliferation organized in sheets and sometimes adopting an epithelial appearance (HES × 100). (b) The cells are medium to large, contained often prominent eosinophilic para-nuclear inclusions (HES × 200). (c) Fine needle aspiration showing a cellular smear with individual cells and clusters of rhabdoid cells, and round cells with eosinophilic cytoplasmic inclusions. (d) Presence of rhabdoid cells arranged in sheets, which are large with abundant cytoplasm and hyaline globular inclusions of intermediate filaments (HES × 400).

large, contained often abundant eosinophilic cytoplasm with prominent eosinophilic para-nuclear inclusions; their nucleus is large, eccentric, round or oval, with mott chromatin and a large nucleolus (**Figure 3(b)**). Immunohistochemically, the tumor cells showed globular cytoplasmic staining for epithelial markers (CKAE1/AE3 and EMA) and vimentin, and a loss of INI-1 nuclear staining (**Figure 4**). The outcome was marked by the increasing size of the frontal mass and the appearance of another peri-auricular mass of 4 cm. In the light of all these clinical, histological, and immunohistochemical features, the diagnosis of "extra-renal rhabdoid tumor" was done and treatment with chemotherapy was started but the child died after 7 weeks.

3.2. Case 2

A 7-month-old boy was admitted for the management of a left subclavicular mass evolving for 40 days. Clinical examination found a huge mass under the left clavicular, extending to the axillary region (**Figure 1(b)**). The CT scan showed a bulky left axillary tumor mass, with lobulated contours, heterogeneously enhanced extending to the cervical region and the proximal portion of the ipsilateral left arm with irregular borders, massively necrotic in the center and vascularized (**Figure 2(b)**). Fine needle aspiration was carried out, showing a cellular smear with individual cells and clusters of rhabdoid cells, and round cells with eosinophilic cytoplasmic inclusions (**Figure 3(c)**). Then, a biopsy was done showing

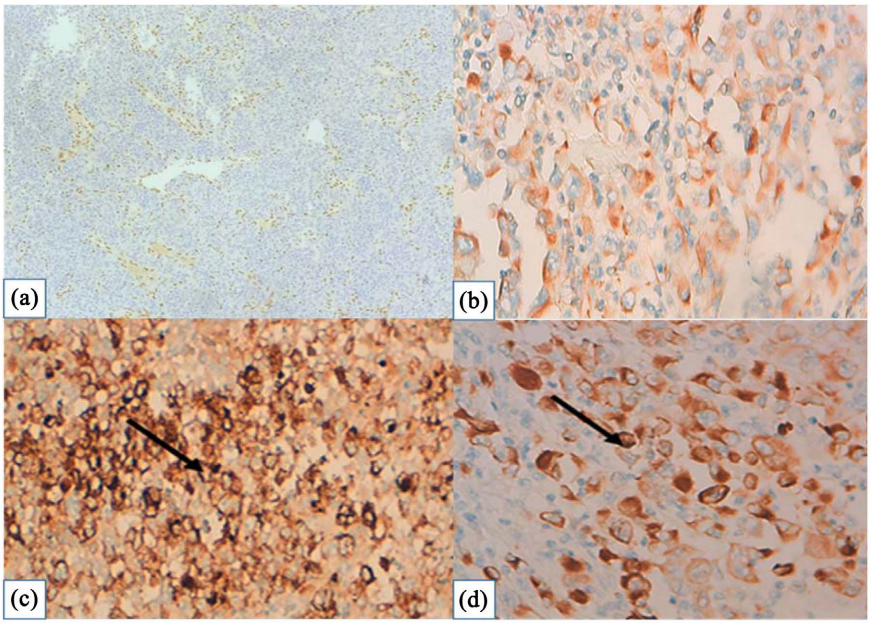

Figure 4. Immuhistochemical staining: (a) Complete loss of INI-1 by tumor cells with internal positif control by endothelial cells. (b) The tumor cells have cytoplasmic positivity with a dot-like pattern for epithelial membrane antigen (EMA). (c) Cytokeratin (CK AE1/AE3). (d) Vimentin.

the presence of rhabdoid cells arranged in sheets, which are large with abundant cytoplasm and hyaline globular inclusions of intermediate filaments, and eccentric vesicular nuclei with large inclusion-like nucleoli (**Figure 3(d)**). On the immunohistochemistry staining, we noted a complete loss of INI-1 by tumor cells. However, the tumor cells have cytoplasmic positivity with a dot-like pattern for epithelial membrane antigen (EMA), CK AE1/AE3, and vimentin (**Figure 4**). The patient was treated with neoadjuvant chemotherapy, however, he was entrusted at the request of his family and subsequently died at home.

3.3. Case 3

A 4-month-old boy presented with a gradually increasing mass in the left eye for 2 weeks. Computed tomography revealed a left intra-conical retro-orbital tumor process responsible for proptosis with a right cerebellar lesion that may be related to a secondary localization (**Figure 2(c)**). We received a biopsy of the mass. The histological analysis and immunohistochemical staining showed the same results as others cases. This patient underwent immediate surgery and then adjuvant Chemotherapy. Subsequently, he installed a quadriventricular hydrocephalus and then died after 8 weeks.

3.4. Case 4

A 2-month-old boy presented with a gradually increasing mass in the left eye for 2 weeks. Cerebral computed tomography revealed a vermian tissue process, spontaneously dense, heterogeneously enhanced, extended to the right cerebellar

hemisphere, and compressing V4 anteriorly (**Figure 2(d)**). We received a biopsy of the mass. The histological analysis and immunohistochemical staining showed the same results as others cases. The patient was treated with neoadjuvant chemotherapy but the child died after 4 weeks.

4. Discussion

Rhabdoid tumor was first identified, in 1978, by Beckwith and Palmer in the kidney as a sarcomatous variant of Wilms tumor [4]. Then, in 1981, Haas *et al.* classified it as a distinct histopathologic entity of kidney tumors. It was called "rhabdoid" originally to the resemblance of this tumor to rhabdomyosarcoma on light microscopic examination and the lack of immunohistochemical and ultrastructural rhabdomyoblastic features led to it being referred to as a "rhabdoid" tumor. Now the rhabdoid features are understood to be cytoplasmic globoid aggregates of keratin and vimentin intermediate filaments [5]. Extrarenal rhabdoid tumor (ERRT) was first reported in 1982 by Gonzalez Crussi *et al.* as "round-cell sarcomas" of infants and young children, in the liver and chest wall [7]. Then, it was described in central nervous system (brain and spinal cord) in 1987 by Biggs *et al.* [8]. Actually, the WHO book defines, morphologically, rhabdoid tumor as a tumor containing a population of "rhabdoid" cells which are large with abundant cytoplasm, perinuclear spherical inclusions, and eccentric vesicular nuclei with large inclusion-like nucleoli, and genetically, by a bi-allelic inactivation of the tumor suppressor gene SMARCB1 (previously named hSNF5, BAF47, and INI-1) located on chromosome 22q11.2, secondary to an inactivating mutations, deletions or duplications of exons, resulting in a stop codon. This is revealed immunohistochemically by a complete loss of nuclear staining of INI-1 [2] [6] [9]. Our four tumors described here shared, in spite of disparate sites, important similarities, all arose in young male infants, and all had rapid growth and were quite voluminous at the time of their detection. Which is comparable to literature data as follows, ERRT is exceedingly rare, develops mostly in children however cases have been reported from new born to teenagers and adults [1]. In an Irish study between 1986 and 2013, the authors found only 4 cases of extrarenal extracranial rhabdoid tumor (EERT) (neck, paravertebral, tongue, and pelvis) out of a total of 25 rhabdoid tumor cases all location included [10]. Atypical teratoid/rhabdoid tumor (AT/RT) accounts for 1.6% off all pediatric CNS tumors and for 10% of CNS tumors in children aged less than 1 year [1] [2]. Rhabdoid tumor of the genital organs and gastro-intestinal tract typically affects older patients (mean age: 63.4 years; age range: 41 - 84 years) [11]. The sex ratio male to female is of 1.2 to 1 [3].

The imaging characteristics of extra-renal rhabdoid tumors are not yet to be determined. Recently, Garces-Inigo *et al.* demonstrated that these tumors have a tendency to be large and hypodense on CT, and show a heterogeneous hyperintensity on T2-weighted (W) magnetic resonance imaging (MRI) [12].

Histologically, rhabdoid tumor is characterized by a sheet of uniform, large

epithelioid cells with vesicular chromatin, prominent nucleoli, and eosinophilic cytoplasm. A subset of cells contains hyaline cytoplasmic "rhabdoid" inclusions as it was defined above. However, there is many variant growth pattern such as myxoid, spindle cell/fascicular, clear-cell pattern, undifferentiated round cells and storiform pattern. Because of this heterogeneous morphology, MRT must be differentiated from rhabdomyosarcoma, epithelioid sarcoma, Ewing sarcoma, anaplastic large-cell lymphoma, melanoma, medulloblastoma and choroid plexus carcinoma. To do the difference between these differential diagnoses, an immunostaining must be done using different antibodies that are summarized in Table 3. Immunohistochemically, rhabdoid tumor displays complete loss of nuclear staining of SMARCB1/INI1, and it stains to smooth muscle actin (SMA), to CKAE1-AE3 (cytokeratin), to epithelial membrane antigen (EMA) and vimentin. This loss of expression of SMARCB1 is not specific for MRTs and it is found in other rare tumors like epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumor, pediatric chordoma [6]. It has been reported that aberrant expression can be classified into three patterns; complete loss, mosaic expression and reduced expression [6].

Regarding therapeutic options, there is no clear consensus; but complete surgical excision remains the treatment of choice whenever feasible, otherwise neoadjuvant or adjuvant chemotherapy often associated with radiation is done. Targeted therapy is under investigation, utilizing various epigenetic pathways including DNA and histone methylation, histone deacetylation, cell cycle arrest and antimitotic mechanisms. Extra-renal MRT demonstrates a rapidly progressive evolution, with metastasis occurring in most patients from 2 to 15 months after diagnosis. It has a dismal prognosis, independent of localization. Disseminated disease to the lungs, lymph nodes, and liver at the time of diagnosis is reported. Death occurs in 80% to 90% of cases after an average period of 5.5 months [2] [10].

Table 3. Differential diagnosis of rhabdoid tumor.

	INI-1	CK	EMA	VIM	MYOGENIN	CD99	CD30	HMB45	NSE
Rhabdoid tumor	Loss	+	+	+	−	−	−	−	−
Rhabdomyosarcoma	+	−	−	+	+	−	−	−	−
Epithelioid sarcoma	Loss	+	+	+	−	−	−	−	−
PNET/ewing sarcoma	+	−	−	+	−	+++	−	−	−
Melanoma	+	−	−	−	−	−	−	+	−
medulloblastoma	+	−	−	−	−	−	−	−	+
choroid plexus carcinoma	+	+	−	−	−	−	−	−	−
Anaplastic large-cell lymphoma	+	−	+	−	−	−	++	−	−

5. Conclusion

Rhabdoid tumor is a rare and aggressive tumor that occurs in children. It should be included in the differential diagnosis of rounds cells tumors of children and thought about in front of any aggressive isolated tumor. The loss of the nuclear staining of INI-1 represents the key to the positive diagnosis in front of rhabdoid morphology. It is a challenging diagnosis for pathologists, especially with tiny biopsy material, or minor rhabdoid components. Despite advances in pediatric oncology, malignant rhabdoid tumors highlight difficulties in therapeutic decisions. We need a large comparative study to open perspectives for new targeted therapies aimed at controlling the inactivation of the SMARCB1 tumor suppressor gene and possibly propose prenatal diagnosis via cytogenetic study.

Ethical Approval

As a retrospective study, and since Ethics Approval is not applicable due to de-identification of data, it is not required in our institution.

Conflicts of Interest

All authors declare that they have no competing interest.

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