Congenital extracranial extrarenal rhabdoid tumor: A rare clinicopathologic entity and diagnostic challenge

Haroula Tsipou, Kleoniki Roka, Maria Gavra, Stavros Glentis, Kalliopi Stefanaki, Antonis Kattamis

ABSTRACT

Introduction: Extracranial extrarenal rhabdoid tumor (EERT) is a rare tumor characterized by highly aggressive behavior. It is mainly observed in infants and young children. Case Report: We report a case of a newborn female infant born with an extensive mass of her left arm at birth. Histological evaluation was consistent with malignant rhabdoid tumor (MRT) with loss of nuclear expression of INI-1/SMARCB1/BAF47 SMARCB1 protein, produced from SMARCB1 gene. Next generation sequencing (NGS) of genomic DNA of the infant revealed a germline de novo fusion c.141C>A (p. Tyr47*), which is pathogenic for rhabdoid tumor predisposition syndrome Type 1 (RTPS1). Despite early administration of chemotherapy, the infant succumbed due to progressive disease at two months of age.

Conclusion: Congenital EERT is a very rare, aggressive entity, with dismal prognosis especially when it develops in a patient with a cancer predisposition syndrome. Timely diagnosis and genetic evaluation are essential for proper management and genetic counseling.

Keywords: Congenital, Rhabdoid tumor, Rhabdoid predisposition syndrome, SMARCB1

INTRODUCTION

Extracranial malignant rhabdoid tumor is a rare, highly malignant, sarcoma-like neoplasm, and frequently lethal disease that typically presents in the kidneys of children [1, 2]. Malignant rhabdoid tumor (MRT) was firstly described in the kidneys as a variant of Wilms’ tumor with rhabdomyosarcomatous characteristics in 1978 [3]. It is currently called MRT when located at the kidneys, atypical teratoid/rhabdoid tumor (AT/RT) at the brain, and extracranial extrarenal rhabdoid tumor (EERT) at other sites of the body such as soft tissues or liver [4, 5]. The exact incidence of RTs is difficult to determine, although a study of 106 children with extracranial MRTs in the United Kingdom calculated the annual incidence to be 0.6 per 1 million children. The incidence was decreasing with increasing age: from 5 per million in the first year of life to 0.04 per million at 10 to 14 years of age.

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Regardless of the anatomic origin, in most cases a biallelic inactivating mutation and/or deletion in SMARCB1 (OMIM # 601607) is found. Furthermore, occasionally RTs are characterized by loss-of-function mutations in SMARCA4 (OMIM # 603254). These genes encode the SMARCB1 (also called INI1 or BAF47) and SMARCA4 (also called BRG1) proteins accordingly. Mutations in these genes result in loss of expression of the encoded proteins which are both members of the SWItch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complexes [7].

Rhabdoid tumors can also be present in a familial setting and almost 35% of these have a germline mutation that predisposes to the disease. Patients with a germline mutation in SMARCB1 have RT predisposition syndrome type 1 (RTPS1; OMIM #609322), whereas those with SMARCA4 germline mutations have RT predisposition syndrome type 2 (RTPS2; OMIM #613325) [7].

Congenital EERTs of the extremities are extremely rare with less than 10 published case reports in English literature. Of interest some of these patients have been initially misdiagnosed as hemangiomas [8, 9].

CASE REPORT

After obtaining informed consent from the parents, we report a case of a female infant, born at 37+6/7 weeks of gestation, after an uncomplicated pregnancy with normal prenatal obstetric ultrasounds and normal delivery. She was the first child of the family. First and second degree family history was unremarkable and non-contributory for cancer predisposition syndrome. There was no history of consanguinity. At birth, physical examination revealed an extensive mass in her left arm. Initial ultrasound was more suggestive of hemangioma, thus, treatment with propranolol was initiated.

As the mass continued to grow, the patient was transferred to a reference center on 9th day of age (Figure 1).

Magnetic resonance imaging (MRI) of left upper arm and shoulder area showed a large, multilobular soft tissue mass extending from left shoulder till the elbow with intrathoracic and supraclavicular invasion. The mass was hyperintense with adjacent muscle in T2-weighted sequences and nearly isointense in T1W (Figure 2). There was restricted diffusion in diffusion weighted imaging, suggestive of hypercellularity. Post-contrast T1W MRI showed mild enhancement of the mass. There were multiple enlarged left axillary, supraclavicular and inferior jugular lymph nodes. Bone invasion was noted. The differential diagnosis suggested by MRI was of a highly aggressive, hypercellular soft tissue tumor such as rhabdomyosarcoma, MRT, infantile fibrosarcoma, peripheral primitive neuroectodermal tumor, and epithelioid sarcoma [10].

Based on these findings, propranolol was discontinued on day 10th of age and surgical biopsy of skin-subcutis ellipse and adjacent axillary nodule was performed. Pathology revealed in the lymph node metastatic deposits of an oxyphilic malignant neoplasm that showed morphological heterogeneity composed of a small cell and a spindle cell component as well. Characteristic features were (a) the considerable number of rhabdoid cells, (b) the loss of cellular cohesion and the brisk mitotic activity, (c) the focal pericellular hyalinization, and (d) the apoptotic necrosis. Since rhabdoid cells can also be observed in other pediatric neoplasms, like alveolar rhabdomyosarcoma, proximal type epithelioid sarcoma, and poorly differentiated chordoma, immunohistochemistry contributes in the precise diagnosis. The parallel detection of epithelial [epithelial membrane antigen (EMA > 70%), keratin 8.18, and keratin 8 (20–30%)], neural (like smooth muscle actin), and myogenic (CD56 and Synaptophysin) markers underlines the polyphenotypic differentiation of the present neoplasm, while the absence of Myogenin/Myf4, MyoD1 discriminates the neoplasm from an alveolar rhabdomyosarcoma. Diffuse membrane expression of CD34, reported in a varying number of RTs was observed. Immunohistochemistry showed loss of nuclear expression of INI-1/SMARCB1/BAF47 SMARCB1 protein, the product of SMARCB1 gene, in all the neoplastic cells, with strongly positive internal controls (endothelial cells and lymphocytes). The loss of the immunohistochemical nuclear expression of INI-1/SMARCB1 protein from all the neoplastic cells is a characteristic feature of AT/RT, renal, and EERTs but it can also be observed in poorly differentiated pediatric chordomas and epithelioid sarcomas proximal type. Finally, there was no detection of Avian v-ets erythroblastosis virus E26 oncogene homolog (ERG), which usually characterizes a proximal type epithelioid sarcoma. In this view, the loss of the nuclear expression of INI-1/SMARCB1 was correlated with the clinical features and the expression of multiple immunohistochemical markers in order to establish the diagnosis of a RT (Figure 3) [11]. Ki-67/MIB-1 was detected in >70% of the nuclei of the neoplastic cells.

Genetic analysis of DNA from peripheral blood revealed SMARCB1:c.141C>A (p. Tyr47*) variant, which is pathogenic for rhabdoid predisposition syndrome type 1. The pathogenic allele was not detected on the patient’s parents and thus was considered de novo (Figure 4).

Because of the age and extent of the mass, surgical excision was not possible. The infant treated with chemotherapy according to EpSSG NRSTS 2005 Protocol Anthracyclines administered despite the neonate’s age. Treatment initiated with VDCy (Vincristine: 0.025 mg/kg/day, Doxorubicin: 1.25 mg/kg/day, Cyclophosphamide: 40 mg/kg/day followed by 2 weekly infusions of Vincristine). Dosing was based on recommendations of the protocol according to age and weight, taking also into consideration the continuing development of kidney and liver function as well as the possible increased

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susceptibility to adverse effects of chemotherapeutics in newborns and infants [12]. Even though, the tumor showed an initial response, progression of disease was noted with occurrence of metastatic pulmonary nodules and further multifocal bone metastasis. During the infants’ treatment, the main therapeutic issues were sepsis due to prolonged neutropenia and inadequate calorie intake. Despite chemotherapy, the infant succumbed two months later due to progressive disease.

**DISCUSSION**

Malignant rhabdoid tumor—firstly described by Beckwith and Palmer in the kidney—is an aggressive, treatment-resistant tumor with rhabdomyosarcomatous characteristics, precocious occurrence (within the first year of life), and aggressive behavior [2, 3, 7].

Initially, it was called “rhabdoid” to imply rhabdomyosarcoma-like features. Malignant rhabdoid tumors are mostly located in the central nervous system...
(AT/RT). They can also be extracranial, located, either in kidneys (RT of the kidney—RTK), or in other soft tissues (EERT [head and neck, paravertebral muscles, liver, mediastinum, retroperitoneum, pelvis, and heart]). They typically metastasize throughout the body and up to 10% have been reported as synchronous tumors [1, 2, 13].

The most frequent extracranial site is the kidney accounting for almost 48% of cases, whereas 14% arise from the head and neck, 13% in the liver, and 25% in a wide range of other sites like the trunk and arms. Imaging studies are not considered particularly helpful in the diagnosis of soft tissue RTs other than to delineate the extent of tumor since the features are nonspecific [6, 14, 15].

Peak incidence is between one and four years of age, although classic RTs in adults are mentioned [14]. Congenital EERTs are extremely rare and have dismal prognosis. Nine cases have been reported so far with congenital EERT of the extremities. In three cases, hemangioma was the initial clinical diagnosis, as also described in our patient. All neonates succumbed in less than six months from diagnosis due to progression of disease, except one patient who passed away on 29 months of age—after second remission—due to sepsis (Table 1) [9, 16, 17–23].

Given the rarity of MRT, the difficulty in differentiating this neoplasm from other soft-tissue sarcomas both clinically and pathologically, and the necessity for prompt treatment to combat the aggressive and rapid nature of tumor growth, a reference center may provide the best chance for optimal outcome [16]. It is important for all implicating specialties to recognize different forms of rapidly growing lesion of the skin, as it will often be a hemangioma, but it could also be an aggressive tumor. The clinical and radiologic diagnosis of congenital hemangiomas when the lesion(s) and imaging are atypical should raise concern, thus the need for a low threshold for skin biopsy in such cases should be highlighted [8, 9].

Rhabdoid tumors are characterized by diffuse proliferation of cells with eccentric nucleus and prominent nucleolus, abundant cytoplasm with eosinophilic inclusion bodies, and distinct cellular membranes. In immunochemistry, RT cells are characterized by increased expression of vimentin (a nonspecific marker), EMA, cytokeratins, as well as loss of SMARCBI protein (a strong indicator for RT). INI1 staining and cytogenetics, fluorescent in situ hybridization (FISH), and/or reverse transcription polymerase chain reactions should be performed on all suspected MRT cases as a confirmatory diagnostic measure. Fluorescent in situ hybridization and cytogenetics are critical to rule out other tumors that can have a similar appearance [11, 16].

Most MRTs demonstrate abnormalities in chromosome 22, regardless of the anatomic location. They develop from loss of function of a member of the SWI/SNF chromatin-remodeling complex that is located at 22q11.2. Different combinations of large interstitial chromosome 22q deletions enclosing the whole gene (in about half of the cases), whole exon duplication or deletion, oligonucleotide insertions, or deletions leading to frameshift and subsequent premature stop codons and nonsense mutations could result in complete inactivation of this tumor suppressor gene [6, 14, 15]. Infrequently MRTs could be caused by loss-of-function mutations in SMARCBI.

| Age/sex | Location | Treatment | Status (age at death) | Reference |
|---------|----------|-----------|-----------------------|-----------|
| 1 d/F*  | Left lower leg | Biopsy/CHT | D (70 d) | Petrof et al. (2020) [9] |
| 3 w/M   | Right upper inner arm + synchronous MRT | Biopsy/CHT | D (5 m) | Luu et al. (2019) [17] |
| 1 d/F   | Left thigh | Biopsy/CHT | D (51 d) | Boudjemaa et al. (2015) [18] |
| 1 d/F*  | Left forearm | Biopsy/amputation, CHT | D (NA) | Frank et al. (2013) [16] |
| 1 d/M   | Left shoulder | Sx | D (7 w) | Toth et al. (2011) [19] |
| 1 d/NA  | Right upper limp | Sx | D (11 d) | Kwon et al. (2009) [20] |
| 1 d/M   | Right thigh | Biopsy, CHT | D (70 d) | Yurdakul et al. (2007) [21] |
| 1 d/F   | Right shoulder | Biopsy | D (6 d) | Stahelin et al. (2000) [22] |
| 1 d/F*  | Left shoulder | Biopsy | D (29 m) | Albrechts et al. (1996) [23] |
| 1 d/F*  | Left arm | Biopsy, CHT | D (2.5 m) | Our patient |

Abbreviations: d: days, w: weeks, m: months, M: Male, F: Female, NA: not applicable, D: dead, CHT: chemotherapy, Sx: Surgery, *Initial diagnosis of hemangioma.
SMARCA4 instead. When familial, in almost 35% of the cases, a germline mutation is present de novo or inherited in an autosomal dominant manner, and a second “hit,” a point mutation or loss of heterozygosity (LOH), at the somatic level, inactivates the wild-type allele and initiates tumorigenesis. Although the penetrance of germline SMARCB1 and SMARCA4 mutations is still unknown, it appears that SMARCA4 mutations are less penetrant for AT/RT than SMARCB1 [7, 15, 24]. Interestingly, germline loss-of-function mutations in SMARCA4 also predispose to small-cell carcinoma of the ovary, hypercalcemic type (SCCOHT) [25]. It has been suggested that all patients who present with RTs be tested for the presence of germline mutations [7]. Relatives of proven germline carriers should also be tested for the familial mutation.

The median age of children with EERT in the setting of rhabdoid tumor predisposition syndrome (RTPS) is younger (5 months) than children with apparent sporadic disease (18 months) [26].

Given the rarity of EERT, disease-specific standardized treatment protocols have not systemically evaluated in randomized trials. Current therapeutic proposals are based on a multimodal approach, combining surgery, chemotherapy, radiotherapy. Anthracycline and actinomycin D have shown to be important chemotherapeutic agents for EERT [27]. Also, alternating courses of the combination of VDCy (vincristine, doxorubicin, and cyclophosphamide) and the combination of ICE (ifosfamide, carboplatin, and etoposide) seem to be effective in metastatic MRT [28].

Addition of autologous stem cell rescue (ASCR) following high dose chemotherapy (HDCT) with melphalan, etoposide, and carboplatin to primary therapy for extracranial MRT remains controversial [6, 29–33]. In ACNS0333 protocol, autologous stem cell transplant is standard of care for ATRT and has been employed in renal MRT in some cases [32]. However, there may be selection bias in the reports of successful use of HDC-ASCR in extra renal MRT. These patients may already be good responders to chemotherapy, thus the addition of the transplant may not be contributing to their better outcomes [30]. Nevertheless, the authors of one recent large case series suggested that this modality could be considered in patients who are good responders to upfront therapy [29]. Despite many attempts to improve these various regimens, EERT is still described as lethal. Limited evidence of improved survival reported [1, 6, 28]. National Wilms’ Tumor Study (NWTS) found 23.2% overall survival (OS) at four years, from a series of 142 cases with malignant rhabdoid tumor of kidney (MRTK) treated between 1969 and 2002 [5]. The 1-year survival was only 31% among 106 children with EERT studied in UK [7]. Furthermore, the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG), Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study, reported 98.4% 3-year OS [28]. The European Rhabdoid Registry (EU-RHAB) suggests the use of multimodal therapy for RTs regardless of anatomic location. Combination therapy includes gross total resection, conventional chemotherapy (vincristine, dactinomycin, cyclophosphamide, doxorubicin, ifosfamide, carboplatinum, etoposide), intrathecal methotrexate, nonrestrictive use of high-dose chemotherapy with stem cell rescue (carboplatinum, thiotepta) and radiotherapy (in individuals age >18 months) [13, 28].

Finally, in the largest published series of 42 European congenital RTs by Nemes et al., overall survival was 12.6%. In this study, conducted on behalf of the European Rhabdoid (EU-RHAB) consortium, significant prognostic factors were gross total resection, therapy according to standardized approach, and complete remission. Presence of germline mutation, inoperability, and metastasis were significant negative factors. Furthermore, it highlighted the special limitations concerning treatment of congenital RTs like prematurity, difficulty to operate, severe toxicity (i.e., vaso-occlusive disease) and role of radiotherapy and its sequelae [13].

CONCLUSION

Management of congenital RTs remains a major challenge due to age, anatomical, and physiologic properties of a developing organism, in combination with presence of frequent negative prognostic factors such as synchronicity, metastases, and higher rates of a germline mutation. Proper pathological and genetic evaluation is required in a timely fashion for optimal therapeutic and counseling interventions. Collaborative trials are required to advance knowledge and to improve efficacy of therapy for these patients.

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Author Contributions

Haroula Tsipou – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kleoniki Roka – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Maria Gavra – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Stavros Glentis – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kalliopi Stefanaki – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Antonis Kattamis – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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