

Rhabdomyosarcoma of the urachus in Costello Syndrome

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Abstract

Costello Syndrome is a rare inherited autosomal dominant disease, characterized by physical and intellectual alterations that include cardiovascular and musculoskeletal abnormalities, growth delay and mental retardation. Diagnosis can be suspected clinically but confirmation requires identification of a heterozygous mutation in the proto-oncogene HRAS. These patients are also more prone than the general population to the occurrence of solid tumors, being the rhabdomyosarcoma (RMS) the malignant tumor more frequent.

We report a case of a 2-year-old boy with Costello syndrome genetically confirmed that presents fever and an acute abdomen. The abdominal ultrasonography suggested an intestinal intussusception. Laparotomy was performed and a large mass related to the urachus was identified and resected. On histology, it was a spindle cell tumor with focal rhabdomyoblastic differentiation. The neoplastic cells expressed myogenin, vimentin, desmin and focally smooth muscle actin. The final diagnosis was an embryonal rhabdomyosarcoma of the urachus.

To our knowledge this is the second case of ERMS of the urachus described in the literature associated with CS.

Keywords: Rhabdomyosarcoma, Urachus, Costello Syndrome

Introduction

Costello syndrome (CS) is a rare autosomal dominant congenital syndrome affecting 200 to 300 people worldwide, and is associated with heterozygous germline missense mutations in HRAS gene and along with other clinically related conditions referred as rasopathies [1-3]. It was first described in 1971 by Costello who reported two children with short stature, redundant skin of the neck,

palms, soles, and fingers, curly hair, papillomata around the mouth and nares, and mental retardation [4]. Others characteristic findings include coarse distinctive facial features, premature aging, developmental delay or intellectual disability, cardiac problems (typically cardiac hypertrophy, less commonly, atrial tachycardia, or pulmonic stenosis) [3]. The predisposition to neoplasia in Costello patients is higher than in the general population, with a tumor frequency that can be as high as 15% and encompasses a spectrum ranging from benign wart-like skin lesions (papillomata) to malignant tumors including neuroblastoma, fibrosarcoma, rhabdomyosarcoma and transitional cell carcinoma of the bladder [3,5]. Rhabdomyosarcoma (RMS), especially the embryonic subtype, is the most frequently encountered

malignant tumor in Costello syndrome [6]. Till now as far as we have searched in PubMed we found 14 cases reported of RMS associated to CS and the majority of them they were all located in the abdominal cavity and pelvis. One of the first reported cases of rhabdomyosarcomas associated to Costello Syndrome was located in very unusual organ, the urachus [7]. The urachus is the embryological remnant of urogenital sinus and allantois. Involution usually happens before birth and urachus is present as a median umbilical ligament. Urachal malignant tumors are extremely rare. The estimated annual incidence of urachal tumor is 0.01% of all cancers in adults and, histologically, adenocarcinoma accounts for 80-90% of the tumors [9]. Although sarcomas represent only 8%, they are the most frequent urachal neoplasms reported in patients younger than 20 years of age [10].

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We report the second known case of a boy with Costello syndrome,

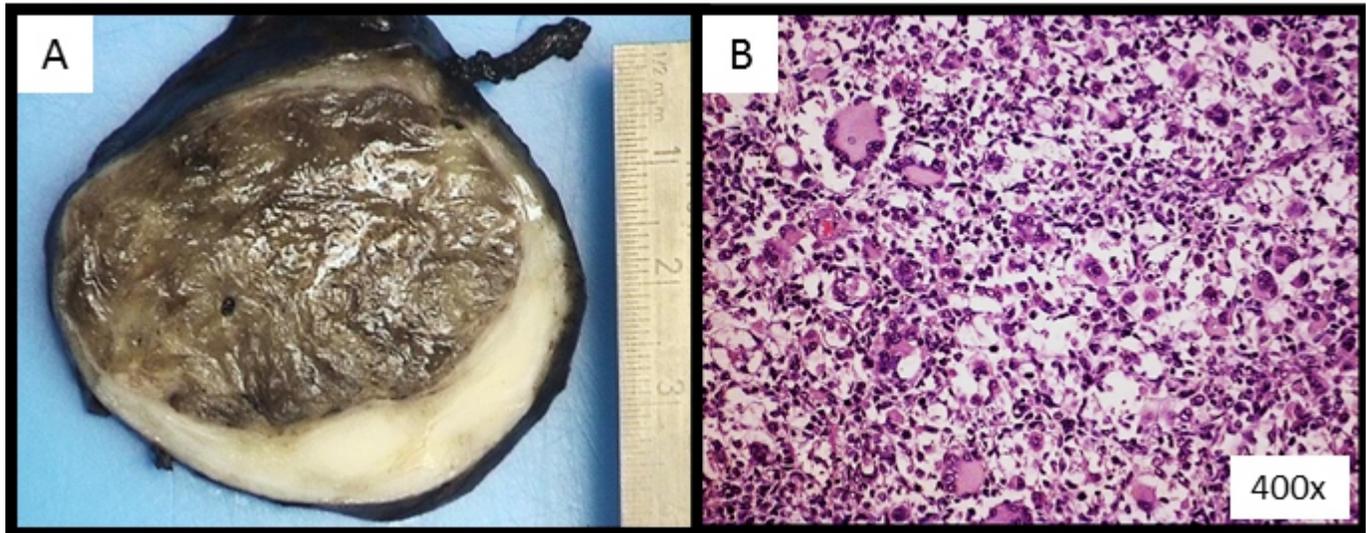


Figure 1: Rhabdomyosarcoma of the urachus: gross (A) and histology (B).

genetically confirmed, that presented an embryonal rhabdomyosarcoma localized in the urachus.

Abbreviations	
CS	Costello Syndrome
RMS	Rhabdomyosarcoma
ERMS	Embryonal rhabdomyosarcoma
SMA	Smooth muscle actin

Case report

A 2-year-old Caucasian boy, of a no consanguineous couple who was diagnosed a macrosomia and polyhydramnios during pregnancy. In the first year of live, he presents severe feeding difficulties that required a gastrostomy. The child presented typical facial characteristics of CS with macrocephaly, coarse face, low set ears and nostrils widened, presence of single

transverse crease, shortening of the fingers, hyperpigmentation of the nipple and areola. It was also noted a growth delay, psychomotor retardation with hypotonia of the lower limbs and cryptorchidism.

Genetic testing identified a heterozygous missense mutation in the exon 2 of HRAS gene, confirming the diagnosis of Costello syndrome.

With two years old, he presents symptoms of acute abdomen and fever. An abdominal ultrasonography suggested the presence of intestinal intussusception, with no other alterations. Laparotomy was performed showing a solid tumor related to the urachus that was completely resected. The tumor weighed 74g and measured 7.5 x 5.3 x 4.6 cm. The cut surface was firm and whitish with a grey central area. On histology, it shows a high

cellularity of spindle cells with pleomorphism and multinucleation (fig.2). No striated cells were identified. The tumor displayed a high mitotic index (> 10 mitoses / 10HPF) and extensive central necrosis. No vascular invasion was seen. The neoplastic cells were expressed myogenin, vimentin, desmin and focally smooth muscle actin (SMA) (fig.2). The histological diagnosis of embryonal rhabdomyosarcoma of the urachus was performed.

Staging procedures showed no metastatic disease and he was staged as a IRS Group I. He was submitted to chemotherapy with four IVA cycles (ifosfamide, vincristine and actinomycin D) and four additional VA cycles (vincristine and actinomycin D). No radiotherapy was administered. Two year after the end of therapy he remains disease-free.

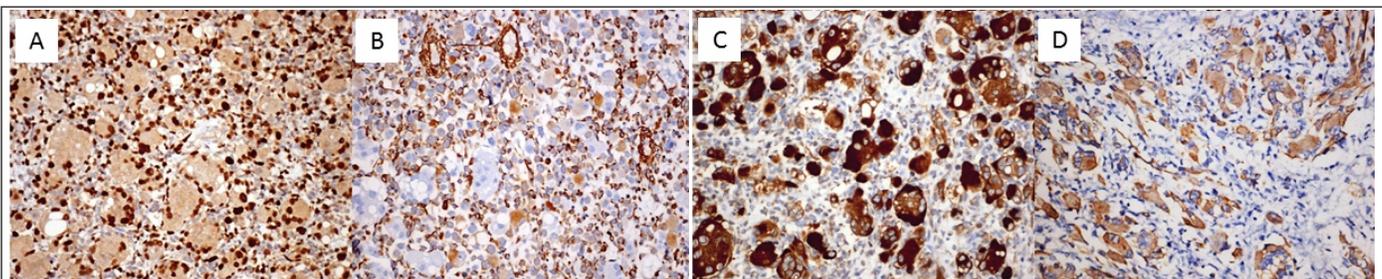


Figure 2: Immunoexpression of myogenina (A), vimentina (B), desmina (C) and smooth muscle actin (D). (200x)

Table 1: Cases of Costello Syndrome and rhabdomyosarcoma

	Our case	Kerr B et al 1998	Bisogno et al 1999	Fiengold et al 1999	Sigaudy et al 2000	Gripp et al 2002	Kawanne et al 2003	Kerr et al 2003
Number of cases	1	2	1	1	1	5	1	1
Sex		1) Male 2) Female	Male	Male	Male	1) Male 2) Female 3) Female 4) Unknown 5) Unknown	Female	Female
Age(s)		1) 2 y 2) 3 y	1 y	6 m	6 y	1) 5 y 2) 3 y 3) 2 y 4) 5 m 5) 1 y	6 m	2 y
Histology	Embryonal RMS	Embryonal RMS	Embryonal RMS	Alveolar RMS	Embryonal RMS	1) Embryonal RMS 2) Pleomorphic RMS 3) Embryonal RMS 4) Embryonal RMS 5) Unknown	Embryonal RMS	Embryonal RMS
Location	Urachus	1) Left psoas muscle 2) Urachus 1) Left psoas muscle	Pelvis	Right foot	Inguinos-crotal	1) Pelvis 2) Upper abdomen 3) Pelvis 4) Perineal 5) Left orbit	Pelvis	Pelvis

Discussion

Costello syndrome can be diagnosed clinically with the presence of some features found in this syndrome like characteristic facial appearance with curly or fine hair, prominent epicanthic folds, long eyelashes, full nasal tip, fleshy ear lobes, and a wide mouth with full lips [3]. Formal diagnostic criteria for Costello syndrome have not been developed, but consensus

guidelines have been published. A suspected clinical diagnosis of Costello syndrome should be confirmed by the identification of the specific germline mutation in the proto-oncogene HRAS. In our case, the boy had a missense mutation of HRAS in exon 2 that confirms the clinic diagnosis. It is the most frequent mutation detects, almost 80–90% of all individuals tested [3]. Patients with Costello Syndrome had a greater

predisposition to develop malignancies, mostly rhabdomyosarcomas. Until now there were described 14 cases of rhabdomyosarcoma associated with this syndrome, and the majority was sub classified in embryonic rhabdomyosarcoma [11-20]. (Table 1) Although rhabdomyosarcoma is the most frequent soft tissue tumor in children, there are very few reports of this tumor rising from the urachus.

Table 2: Cases of embryonic rhabdomyosarcoma of the urachus

Case Report	Age	Sex	Symptoms	Stage	Resection	Tumor size (cm)	Treatment	Genetic abnormality known
Ransom H (1933)	4 month	Female	Abdominal mass	Stage III	R0	11,5	Surgery	—
Yokoyama S et al (1997)	2 years	Male	Abdominal pain	Stage III	R1	9,0	Surgery + chemotherapy (cyclophosphamide, vincristine, and dactinomycin)	—
Kerr B et al -1998	3 years	Female	Abdominal mass	—	R1	—	Surgery + Chemotherapy:ifosfamide, actinomycin and vincristine	Costello syndrome (no molecular testing)
Schulz and O’Leary (2001)	2 years	Male	—	Stage III	R0	—	Surgery + chemotherapy + Radiotherapy	Neurocutaneous syndrome?
Fernandez E. and al (2007)	6 years	Female	Intractable constipation + painless suprapubic mass	Stage III	R0	13,5	Surgery + Chemotherapy (ifosfamide, vincristine, and dactinomycin)	—
Letelier N et al (2008)	3 years	Male	Acute abdomen	Stage III	R0	6,0	Surgery + Chemotherapy (ifosfamide, vincristine, and dactinomycin) + radiotherapy	—
Our case	2 years	Male	Acute abdomen	Stage III	R0	7,5	Surgery + Chemotherapy (vincristine)	Costello Syndrome (HRAS mutation detected)

Urachal malignant tumors are rare and only 6 cases of embryonic rhabdomyosarcoma was reported and just one of them was associated to Costello Syndrome [10, 21-24] (Table 2)

The diagnosis of rhabdomyosarcoma can be done by the presence of

myoblastic cells that express myogenina or myo D1. Other markers like desmina, vimentina and SMA can be positive but they are not specific. Due to the greater probability of developing malignant tumors, these children will certainly benefit with a special screening plan using an imaging

control. This plan will have to begin early in life, because the appearances of these tumors typically occur in very young ages. Besides, sooner we detect the tumor, more quickly we can start the treatment.

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Conflict of Interest: NIL

Source of Support: NIL

Informed consent of the patient was taken for publication

How to Cite this Article

Costa J, Succeso M B, Barroca H. Rhabdomyosarcoma of the urachus in Costello Syndrome. *Journal of Bone and Soft Tissue Tumors* Sep - Dec 2016;2(3):21-24.