

Case Report

Medulloepitheliomatous component of immature teratoma lacks amplification at chromosome 19q13.42 locus: report of a case

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Abstract: Medulloepithelioma is a rare embryonal tumor of the central nervous system (CNS). Its distinct appearance is characterized by papillary and tubular arrangements of malignant single- to multi-layered columnar epithelium surrounded by an outer basement membrane. For years, this tumor has been viewed as an embryonal tumor that recapitulates the earliest stage of CNS development, namely the neural tube stage. Recently, amplification in 19q13.42 classified medulloepithelioma with ependyoblastoma and embryonal tumor with abundant neuropil and true rosettes (ETANTR) under the umbrella term embryonal tumor with multilayered rosettes (ETMR). Medulloepitheliomas typically occur in the cerebral hemispheres, but also uncommonly involve the cerebellum, cauda equina, presacral region, and eye. Medulloepitheliomatous elements can also arise in teratomas of the sacral and presacral region, raising a question as to how they compare to genuine CNS medulloepitheliomas that harbor the signature 19q13.42 amplification. We report a case of ventral sacrococcygeal immature teratoma with a prominent medulloepitheliomatous component arising in an 11-month-old girl as a ventral sacrococcygeal tumor with intra-spinal extension from T10 to S3. Following surgical resection, the tumor recurred seven years later in the same location. The recurrent tumor consists almost exclusively of the medulloepitheliomatous component present in the original tumor. Additionally, the recurrent tumor lacks amplification in 19q13.42 by fluorescent *in situ* hybridization (FISH), suggesting that extracranial medulloepitheliomas are biologically different from conventional medulloepithelioma tumors despite their morphologic resemblance.

Keywords: Medulloepithelioma, teratoma, sacrum, embryonal tumor with multilayered rosettes, 19q13.42 locus

Introduction

Medulloepithelioma was first established as an entity by Karch and Urich in 1972 [1]. A rare tumor, its distinct histological hallmarks are papillary, tubular, or ribbon-like arrangements of neoplastic pseudostratified columnar epithelium surrounded by an outer limiting membrane, thus resembling the early neural tube stage of the developing nervous system at four- to ten-weeks of gestation [1-3].

Medulloepithelioma is classified as an embryonal tumor of the central nervous system (CNS) of histologic grade IV in the 2007 *World Health Organization (WHO) classification of tumors of*

the central nervous system. Additionally, medulloepithelioma shares many clinical, radiological, and morphologic features with other CNS embryonal tumors, specifically ependyoblastoma and embryonal tumor with abundant neuropil (ETANTR). Recent studies have grouped these three entities under the umbrella term embryonal tumor with multilayered rosettes (ETMR) after the discovery of a shared amplified locus at chromosome 19q13.42 (involving the *C19MC* cluster of microRNA) and immunoreactivity for the protein LIN28A [4, 5] among these three entities.

Medulloepithelioma occurs most commonly in the cerebral hemispheres of children younger

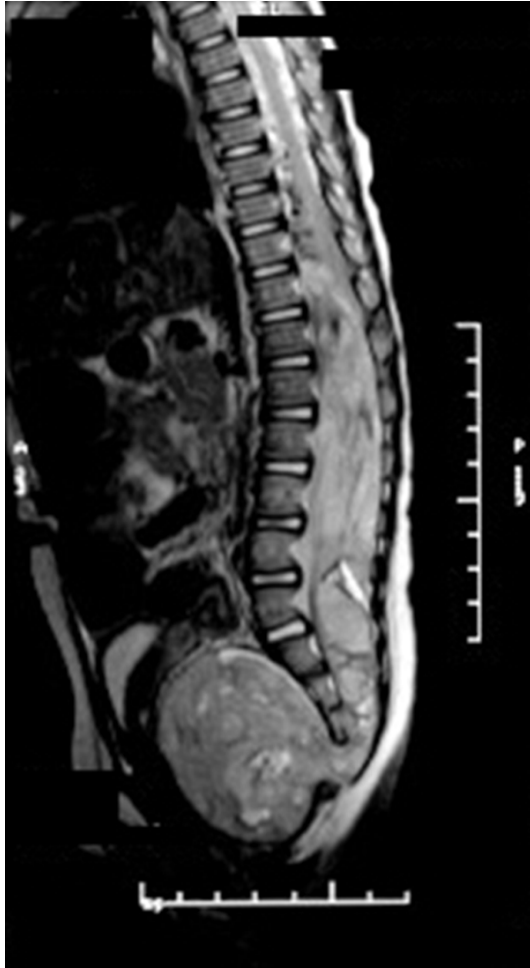


Figure 1. T2-weighted image demonstrated a large presacral mass with invasion and extension into the lower lumbar and sacral spine.

than five years of age [2] but rarely involves the cerebellum, presacral region [1, 6-9], peripheral nerve [10], pelvis [11], testis [12-14], ovary [12, 15], and eye [16-19]. CNS medulloepithelioma has a poor outcome with demise occurring commonly in less than 12 months from diagnosis [2]; extracranial presentations, however, are generally more favorable in prognosis [20]. In the original cases described by Karch and Ulrich [1] where medulloepithelioma was established as an entity, all but one case was fatal; the sole survival case arose from the sacrum.

Clinical and behavioral discrepancy between intracranial and peripheral (extracranial) presentation may suggest that these tumors are biologically different despite their similar morphology. Here, we report a case of immature teratoma with a prominent medulloepithelio-

matous component that lacks the signature chromosomal 19q13.42 amplification of ET-MRs.

Clinical presentation

The infant presented at age 11 months on March 2004 with a very rapid onset loss of strength in the lower extremities that progressed to flaccidity. Magnetic resonance imaging (MRI) revealed a 5.5 × 3.8 × 4.5 cm, well-defined mass in the ventral presacral region. The mass appeared as a ventral sacroccocygeal tumor with intra-spinal extension from T10 to S3, displacing the bladder anteriorly and surrounding the spinal cord posteriorly. The levels S4-S5 and coccygeal elements of the bony spine were obscured from visualization, secondary to either hypoplasia or tumor destruction. The mass contained large solid areas with enhancement, fat signal intensity, and calcifications. The remainder of the spinal cord superior to the aforementioned lesion was unremarkable (**Figure 1**).

This tumor was resected via an anterior and posterior approach. After surgery, the patient regained all of her strength and mobility, but was left with urinary retention and constipation. There was no recurrence or residual tumor as per imaging for three years, and she was released for routine follow up.

She remained well except for symptoms of neurogenic bladder and constipation until six years and four months later, in July 2010, when she complained of abdominal pain and left hip pain. She was diagnosed with severe constipation and “an enlarged kidney”. She again presented in February 2011 (almost seven years after her original diagnosis) with back and abdominal pain. MRI showed a 6.0 × 1.4 cm intradural, heterogeneously enhancing mass spanning from T10 to L2 levels of the spinal cord. Imaging studies of the brain and abdomen were normal; no metastases were identified. There was no increase in serum α -fetoprotein. The tumor was resected again and the patient had no evidence of disease since. Follow up local proton therapy treatment with 50.4 CGE was performed. She tolerated both surgery and radiation with no change in neurologic sequelae. She was last evaluated three years after completion of therapy and had no evidence of disease locally or throughout the craniospinal axis.

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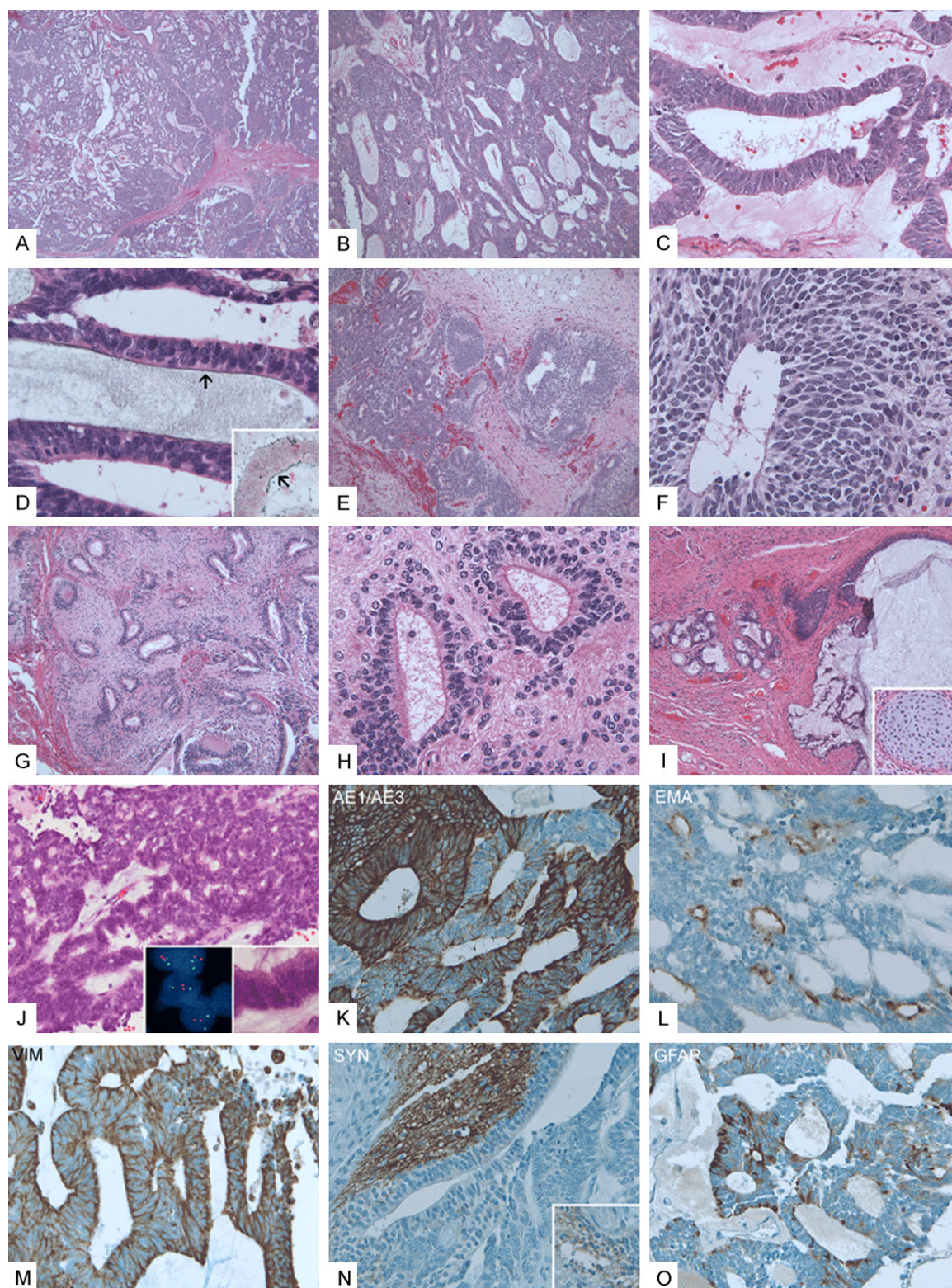


Figure 2. (A, B) Part of the specimen is composed of an epithelial neoplasm arranged in ribbons with lumen formation. (C) The tumor cells are columnar, have hyperchromatic nuclei and high nuclear-to-cytoplasmic ratios. (D) Basement membrane-like material is demonstrated on the abluminal side of the tumor cells by Jones stain (arrow) where reticulin deposition is also demonstrated by reticulin stain (arrow in inset). (E, F) In other areas of the tumor, the epithelial component forms multilayered rosettes surrounding luminal structures, which resembles primitive neuroectoderm. (G, H) Numerous areas reminiscent of ependymal canals are present, surrounded by immature

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glioneuronal tissue. (I) Mucin-secreting glands and cartilage (inset) are noted in a small area of the tumor. (J) The recurrent tumor is very similar to the medulloepitheliomatous component of the original resection and shows single layered high columnar cells (inset). Fluorescent *in situ* hybridization (FISH) is negative for amplification at chromosome 19q13.42 locus (inset). (K) Cytokeratin AE1/AE3 is widely expressed in the medulloepitheliomatous component. (L) Immunoreactivity for epithelial membrane antigen is noted in areas resembling ependymal canals. (M) Many tumor cells are positive for vimentin. (N) Focal immunoreactivity for synaptophysin is noted in both non-medulloepitheliomatous and medulloepitheliomatous (inset) tumor cells. (O) Focal immunoreactivity for GFAP is also present in the medulloepitheliomatous component. Original magnification in (A) is 2 ×; (B, E, G, I) is 10 ×; (O) is 20 ×, (J, K, L, M, N) and inset in (N) is 40 ×; (C, D, F, H), and insets in (D), and (O) is 60 ×.

Of note, her father was diagnosed with tethered cord sometime after her diagnosis.

Pathology

First resection

The specimen consisted of multiple fragments of pink-tan, irregular tissue ranging from 1.0 × 0.5 × 0.5 cm to 10.0 × 3.0 × 2.0 cm with a gray, mucoid cut surface, and focal hemorrhage; the specimen was entirely submitted in 28 tissue blocks.

Histologically, a large focus of medulloepitheliomatous component comprised about three tissue blocks. These areas showed a ribbon-like and tubular epithelial proliferation mimicking a carcinoma (**Figure 2A-C**). Neoplastic epithelial cells were lined by a layer of basement membrane, demonstrated by Jones stain (**Figure 2D**) and periodic acid Schiff (PAS) stain with diastase pretreatment. Reticulin fibers were also noted in the basement membranes (**Figure 2D**, inset). The luminal aspect of the ribbons and tubules lacked cilia. The periphery of these tubules also showed maturation into glial and neuronal cells. Other areas of the tumor contained neural tube-like structures composed of primitive cells that varied from multi-layered (**Figure 2E** and **2F**) to single-layered (**Figure 2G** and **2H**). There were also tubules that resembled ependymal canals, which were only one or two cell layers thick with occasional cilia. Overall, the tumor contained only a small amount of non-neuroepithelial component via cartilage and epithelium, including mature skin with hair and mucin-producing epithelium (**Figure 2I**). Although composing only a minute amount of tumor volume (about one tissue block in total of 28 blocks), the mature components confirmed the teratomatous nature of this tumor. Other germ cell components (seminoma, yolk sac tumor, embryonal cell carcinoma, or choriocarcinoma) were absent. The

tumor was diagnosed as immature teratoma with medulloepithelioma component.

Second resection

The medulloepitheliomatous component composed the bulk of the resected material (**Figure 2J**), with complete absence of non-neuroepithelial elements. Histologically, the tumor resembled the medulloepitheliomatous component of the first resection, containing ribbon and cribriform arrangements of malignant epithelial cells. Maturation with amorphous calcifications were present and focal areas contained melanin pigment deposition. Maturation into neural tissue similar to that noted in the first resection was also present. Neither immature nor mature component demonstrated necrosis. No evidence of yolk sac tumor or embryonal cell carcinoma was identified; no increase in serum α -fetoprotein was noted.

Molecular pathology study

Fluorescent *in situ* hybridization (FISH) was performed on the second resection to detect focal amplification at chromosome 19q13.42 locus and the result was negative (**Figure 2J**, inset). Dual-color FISH was performed on 4 μ m paraffin embedded tissue sections. Probes were derived from BAC clones (BACPAC Resources, Oakland, CA) and labeled with either AlexaFluor-488 or AlexaFluor-555 fluorochromes (Invitrogen, Carlsbad, CA). The following BACs were used to assess copy number abnormalities (CNAs) at *MIR517C* genetic loci of interest: *MIR517C* at 19q13.4, RP11-984E8 (19p controls CTD-2538G9 and CTD-2528A14). All probe mixtures were diluted 2:50 in hybridization buffer and co-denatured with the target cells on a slide moat at 90°C for 12 minutes. The slides were incubated overnight at 37°C on a slide moat and then washed in 4 M Urea/2xSSC at 25°C for 1 minute. Nuclei were counterstained with DAPI (200 ng/ml) (Vector

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Labs) for viewing on a Olympus BX51 fluorescence microscope equipped with a 100 watt mercury lamp; FITC, Rhodamine, and DAPI filters; 100 × PlanApo (1.40) oil objective; and a Jai CV digital camera. Images were captured and processed with an exposure time ranging from 0.1-2 seconds for each fluorochrome using Cytovision v4.5 software from Leica Biosystems (Richmond, IL).

Immunohistochemistry

Immunohistochemistry study for vimentin (Clone 3B4, Ventana, Tucson, AZ), S100 protein (Polyclonal catalog number 760-2523, Ventana, Tucson, AZ), epithelial membrane antigen (EMA) (Clone E29, Cell Marque, Hot springs, AR), glial fibrillary acidic protein (GFAP) (Clone EP672Y, Cell Marque, Hot springs, AR), synaptophysin (Clone SP11, Ventana, Tucson, AZ), cytokeratin AE1/AE3 (Clone AE1/AE3/PCK26, Ventana, Tucson, AZ), neurofilament (Clone FNP7, Invitrogen, Camarillo, CA), NeuN (Clone A60, Millipore, Temecula, CA), and Ki67 (Clone 30-9, Ventana, Tucson, AZ) were performed with a Benchmark automated stainer (Ventana, Tucson, AZ) with antigen retrieval and dilution recommended by the vendor.

In the medulloepitheliomatous component from the first resection, about 75% of the tumor cells were extensively immunoreactive for cytokeratin AE1/AE3 (**Figure 2K**). The luminal surface of most tubules was focally immunoreactive for EMA (**Figure 2L**). Almost all tumor cells were variably positive for vimentin (**Figure 2M**). Only focal immunoreactivity was demonstrated for synaptophysin (**Figure 2N**) and S100 in both the glioneuronal component and, even less commonly, the epithelial component. Only occasional immunoreactivities for GFAP (**Figure 2O**) and neurofilament were noted. The tumor cells were negative for NeuN. The Ki67 labeling index was about 50% in the medulloepitheliomatous component. The immunohistochemistry of the second resection mirrored that of the first resection except that the highest Ki67 labeling index reached approximately 75% in the medulloepitheliomatous component but only 1-2% in areas with maturation.

Discussion

We present a case of medulloepithelioma arising in a sacral immature teratoma that recurr-

ed six years following resection. The tumor was responsive to surgery and proton therapy with no recurrence since. Both occurrences contained a medulloepitheliomatous component that is classic in morphology and immunohistochemical profile in accordance with the current diagnostic criteria for CNS medulloepithelioma [1-3]. Medulloepitheliomas morphologically recapitulate the neural tube stage of CNS development. This characteristic was also reflected by the positive immunohistochemical expression of epithelial markers, particularly cytokeratin. Neuroendocrine markers and neuronal markers are often negative or only focally positive. These features were all present in the medulloepitheliomatous component of the teratoma under discussion.

Despite this histologic resemblance with classic intracranial medulloepithelioma, however, FISH studies on the recurrent tumor lacked amplification of the chromosome 19p13 locus that is characteristic of conventional CNS medulloepithelioma and other embryonal tumors with multilayered rosettes (ETMRs) [4, 5]. This finding suggests that intracranial medulloepithelioma and peripheral (extracranial) medulloepithelioma may represent two groups of tumors with shared phenotypic and histologic characters, but different tumorigenic mechanisms and biological behavior.

Extracranial presentations of medulloepithelioma include sacrum and presacral region [1, 7-9], peripheral nerve [10], pelvis [11], and eye [16-19]. Authors speculated initially that tumors in these locations arose as primary neoplasms from vestigial remnants of the medullary tube [7, 8], while other authors postulate teratomatous origins [9, 20]. Embryonal tumors, including medulloepithelioma, are well-documented in the testis and ovary, where they represent neural components of mixed germ cell tumors [12-15] and, rarely, malignant mixed mesenchymal tumors [21].

Distinction between *de novo* and teratomatous origin is obscured somewhat by multipotential differentiation in CNS medulloepithelioma, which is known to diverge focally along neuronal, glial, or ependymal cell lines, or even contain heterologous mesenchymal elements such as bone, cartilage, and striated muscle [22]. In these circumstances, however, extracranial

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medulloepithelioma is still considered a primary malignancy as long as its embryonal component accounts for the vast majority of the tumor [15].

Our case from the sacrum falls into this category of predominant medulloepithelioma with rare teratomatous components. Nine other cases arising from the sacrum or presacrum have been described in the literature [1, 6-9, 11, 20, 23], with age of presentation ranging from perinatal to 17 years of age. Distant metastases involved five cases [7-9], of which four died from disease [7, 8]. The four remaining presentations were limited to the primary site and showed no evidence of disease on follow-up, including one in which the tumor was treated with chemotherapy following incomplete resection [20]. Of note, the original sacral medulloepithelioma reported by Karch and Urich [1] was also considered a pure medulloepithelioma.

Medulloepithelioma associated with gonadal tumors shows similar prognoses to sacral medulloepithelioma. In four cases of primary ovarian medulloepithelioma, Kleinman *et al.* reported two patients showing survival beyond three and nine years follow-up, while two others developed metastases with subsequent demise [15]; additionally, Michael *et al.* reported that patients showed excellent survival when medulloepitheliomatous components were confined to the testes [13].

Overall, extracranial medulloepitheliomas showed a guarded, but more favorable prognosis when compared their CNS counterparts [20]. This clinical and behavioral discrepancy may be reflected in differences in tumor biology. Ulbright *et al.* showed that testicular PNETs differed by genetic signature when compared to their traditional counterparts. Notable examples included Ewing sarcoma-like PNET lacking *EWS* gene rearrangements and a testicular medulloepithelioma showing FISH positivity for chromosome 22 translocation. The authors thus speculated that testicular versions of PNETs were unlikely to be true representations of their counterparts described in more conventional locations [14].

Intraocular presentation of medulloepithelioma has also been described recently to show diverse molecular patterns, thus expanding

upon the biological mechanisms thought to give rise to medulloepitheliomatous histology. Jakobiec *et al.* reported that intraocular medulloepithelioma lacked amplification of chromosome 19q13.42, in contrast to conventional CNS medulloepithelioma [24]. And although most intraocular medulloepitheliomas expressed LIN28A immunoreactivity akin to their CNS counterparts, findings suggested that protein expression was more closely related to aggressive tumor behavior rather than to tumorigenesis [24]. Additionally, intraocular medulloepithelioma has been shown to harbor D1709N mutations in *DICER1* both in somatic cases [19] and in association with pleuropulmonary blastoma [25]. Overall, prognosis in intraocular tumors is favorable after complete enucleation [10, 16], although it remains unclear whether anatomic stage or biological constitution is most responsible for differences in prognoses [24].

Our current case is a rare presacral teratoma with a prominent medulloepitheliomatous component as determined by classic histopathologic criteria and immunohistochemical profile. It lacks the 19q13.42 amplification of CNS medulloepithelioma and other ETMRs. To our knowledge, this is the first sacral medulloepithelioma evaluated by this molecular study. Taking into account molecular findings in gonadal-associated and intraocular presentations, we propose that medulloepithelioma probably represents a family of tumors with shared phenotypic and histologic characteristics but potentially different tumorigenic mechanisms and biological behavior.

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Disclosure of conflict of interest

None.

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