

Metastatic primary brain rhabdomyosarcoma in a pediatric patient: illustrative case

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BACKGROUND Primary intracranial rhabdomyosarcoma is an extraordinarily rare malignant tumor, with even fewer presenting with distant metastasis. To date, only five cases, including the one presented here, have been reported to present metastatic activity.

OBSERVATIONS A 12-year-old boy presented with a few days of headache, nausea, vomiting, but no neurological deficit. Brain computed tomography and magnetic resonance imaging demonstrated hydrocephalus and a cystic lesion with left parieto-occipital extension. After resection, pathology reported primary rhabdomyosarcoma, with positive desmin and myogenin on immunohistochemistry. The patient presented with pulmonary metastasis. The patient had an overall survival of 21 months after diagnosis with optimal treatment.

LESSONS Rhabdomyosarcoma is a malignant neoplasm arising from undifferentiated skeletal muscle cells, with morphological, immunohistochemical, ultrastructural, or molecular genetic evidence of primary skeletal muscle differentiation. It presents with a rapidly worsening clinical course and the final outcome is poor. Treatment is widely based on protocols that have been proven to be effective in extracranial versions of these tumors, although repeatedly ineffective. Primary brain rhabdomyosarcoma poses a diagnostic challenge because of its infrequent presentation, grade of undifferentiation and tumor heterogeneity. Immunohistochemical and genetic testing have proven to be useful tools for diagnosis.

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KEYWORDS rhabdomyosarcoma; brain tumor; metastasis

Primary intracranial rhabdomyosarcoma is a rare malignant tumor. To our knowledge, to date, there are only 51 cases of rhabdomyosarcoma in pediatric patients, including the present case, reported in the literature.¹ Only five reported this metastatic activity.

Due to its undifferentiated nature, this type of tumor poses a diagnostic and therapeutic challenge to the treating team.

Here, we present the case of a 12-year-old boy with primary brain rhabdomyosarcoma (PBRMS) who developed pulmonary metastasis, as well as a discussion with a review of literature in pediatric patients with this type of tumor.

Illustrative Case

A 12-year-old boy presented with a few days of headache, nausea and vomiting, personality changes as well visual changes; prolonged

verbal response latency was found. He was brought to the attending physician who ordered a brain computed tomography (CT) scan, which demonstrated ventricular enlargement and a heterogeneous left parieto-occipital lesion. Contrast magnetic resonance imaging (MRI) of the brain (Fig. 1) documented an intraventricular lesion with invasion of left occipital and parietal brain parenchyma, mass effect, and ventricular enlargement.

Resection of the lesion was performed through a left parieto-occipital craniotomy, with a parietal transcortical transventricular approach, finding a grayish, friable, well-vascularized tumor. His symptoms resolved postoperatively.

The specimen was sent to pathology, but the diagnosis was unclear, thus, an interdepartmental opinion was consulted. The final histopathological report determined that the tumor was characterized by

ABBREVIATIONS CT = computerized tomography; ECOG = Eastern Cooperative Oncology Group; EU-RHAB = European Rhabdoid Registry; MRI = magnetic resonance imaging; PBRMS = primary brain rhabdomyosarcoma; PET = positron emission tomography; RMS = rhabdomyosarcoma; VAC protocol = vincristin, dactinomycin, cyclophosphamide protocol.

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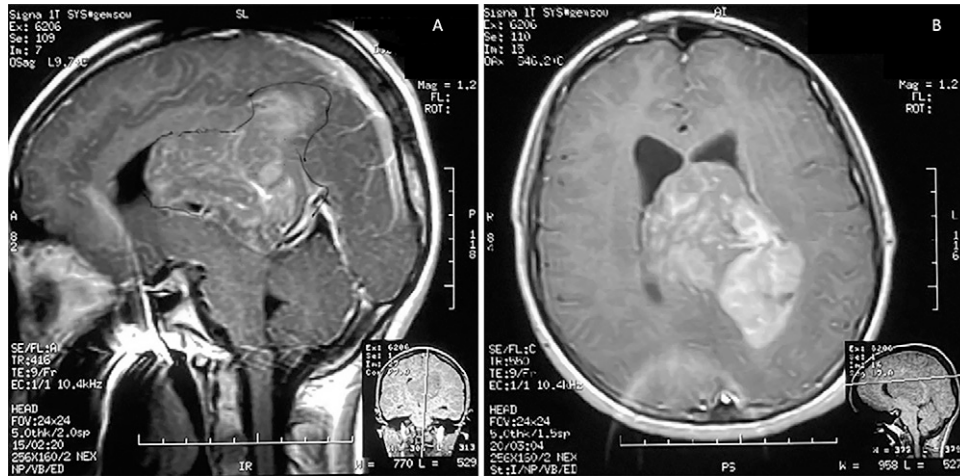


FIG. 1. Sagittal (A) and axial (B) contrast MRI showing an intraventricular lesion with invasion of left occipital and parietal brain parenchyma, mass effect and ventricular enlargement.

numerous homogeneous neoplastic cells, with prominent hyperchromatic, slightly elongated nuclei surrounded by a scant clear cytoplasm, occasionally organized in a perivascular pattern (Fig. 2). Immunohistochemical studies demonstrated the absence of early neuronal markers, and glial fibrillary acidic protein and epithelial membrane antigen were negative. Immunohistochemistry for desmin was strikingly robust in practically every single neoplastic cell and the myogenin, although weak, was also expressed by some neoplastic cells. The neural cell adhesion molecule (CD56) was also positive (Fig. 3). The presence of this immunophenotype, even in the absence of actin immunoreactivity, was diagnostic of a sarcomatous tumor, with muscle differentiation, compatible with an embryonal rhabdomyosarcoma, primary of the brain. CD56 and C68 were positive.

The patient received postoperative radiotherapy with 63 Gy in two phases with volume-security margin and reinforcement to the surgical bed with previous administration of temozolomide as a radiosensitizer and remained free of recurrence for 11 months.

Control MRI revealed a neoplastic lesion inside the left ventricle, as well as occupation of the midline, with images compatible with radionecrosis. A temporal left lesion was demonstrated, which had invasion into the hippocampal region, as well as new lesions in the subarachnoid space surrounding the brainstem and the cerebellum

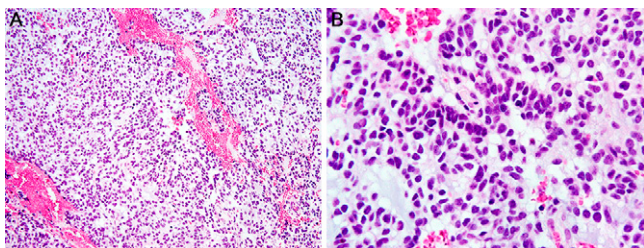


FIG. 2. Hematoxylin and eosin, original magnification $\times 20$ (A) and $\times 60$ (B). Sheets of neoplastic cells were mixed with extensive areas of hemorrhage and a net of underlying blood vessels. Occasionally the cells were arranged in a perivascular pattern. With this histological pattern, the differential diagnoses include a supratentorial primitive neuroectodermal tumor, a clear cell ependymoblastoma and a sarcomatous tumor.

that were not previously described. The patient underwent subtotal resection, with 95% of resection due to splenium invasion.

One month later the patient developed intracranial hypertension, and it was decided to install a parieto-occipital ventriculoperitoneal shunt. The patient had a total recovery.

Six months thereafter, the latest positron emission tomography (PET) was performed, documenting findings of new cervical ganglia with metabolic uptake in compartments IIA and V bilaterally and another lymph node with uptake in cervical level VA, a mediastinal lymph node and three pseudonodular lesions in the right lung, compatible with metastatic activity (Fig. 4). There was new evidence of an intracranial lesion, so a meningeal biopsy was performed, confirming findings similar to the previous lesion; therefore, palliative measures were taken. The patient had an overall survival of 21 months after diagnosis.

Discussion

Observations

PBRMS is an extremely rare malignant tumor, arising from undifferentiated skeletal muscle cells that shows morphological, immunohistochemical, ultrastructural, or molecular genetic evidence of primary skeletal muscle differentiation.^{2,3} Only sporadic cases of PBRMS have been reported in the literature (Table 1).⁴⁻⁶ In fact most of the central nervous system (CNS) localizations are usually metastatic,³ usually secondary to direct extension into parameningeal or paraspinal sites.⁷

PBRMS is found more often in young adults, with a mean age at the time of diagnosis ranging from 20 to 65 years old.⁸ Among these primary brain sarcomas, 70% arise in the pediatric population and there have been limited cases reported in adults.⁵ These scarce cases may be due, partly, to histological and anatomical uncertainty.³

Rhabdomyosarcoma (RMS) is historically classified based on histopathological features into distinct clinical subtypes: embryonal RMS, alveolar RMS, pleomorphic, and spindle cell and sclerosing RMS. Embryonal RMS represents the majority of cases and is associated with a favorable prognosis, while alveolar RMS is more clinically aggressive due to a propensity for metastasis and recurrence.⁹

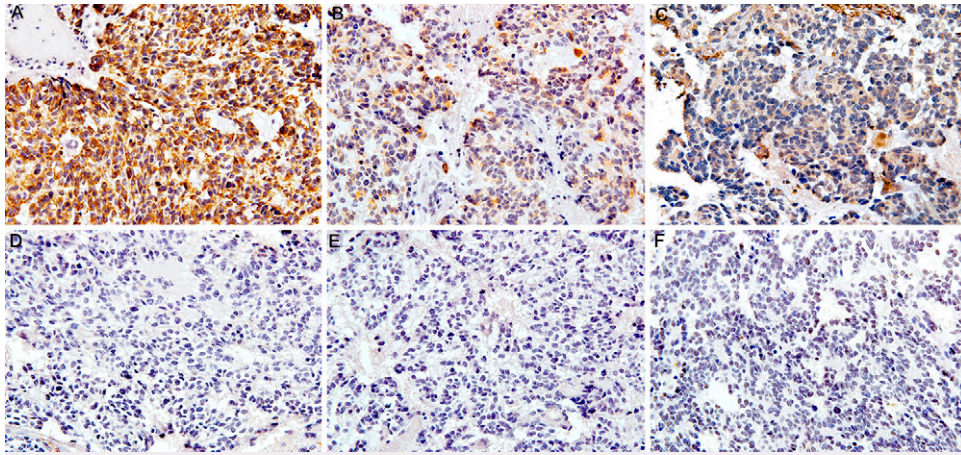


FIG. 3. The immunohistochemistry for desmin was strikingly robust in practically every single neoplastic cell (A), and the myogenin, although weak, was also expressed by some neoplastic cells (B). S100 was mildly positive (C). Glial fibrillary acidic protein and epithelial membrane antigen (D and E) were negative, excluding a glial or ependymal tumor. The immunohistochemical studies demonstrated the absence of early neuronal markers such as synaptophysin and phosphoneurofilaments (SMI-35 and SMI-312; F). Original magnification $\times 40$.

According to Biggs et al.¹⁰ PBRMS are often depicted as diffuse lesions comprising homogeneous, large, round, or polygonal neoplastic cells, densely packed and sometimes arranged in columns, with eccentrically located nuclei and abundant, eosinophilic cytoplasm.

The CNS variant, similar to other high-grade brain tumors, presents with frequent mitotic figures, with positive immunostaining for Ki-67 proliferative labeling index, with a string reaction for epithelial membrane antigen, vimentin, desmin, myoD1, and more focally myogenin. RMS highlights, regardless of the location, with deletions and/or mutations of SMARCB1/INI1, a tumor suppressor gene located in chromosome band 2¹¹q11.2.¹¹

It presents with a rapidly worsening clinical course and the final outcome is poor. Average survival is 9.1 months and only three patients

have survived for more than 24 months. One case reported by Celli et al.¹² reported a patient with a 30-month disease-free period after treatment with surgery and adjuvant radiotherapy and chemotherapy.

The presentation in our patient is an unusual one, since its initial clinical picture included intracranial hypertension and obstructive hydrocephalus secondary to cerebral aqueduct occlusion from a very large intraventricular tumor.

Lessons

Regarding treatment, it is widely based on protocols that have proven to be effective when used for RMS in other anatomical locations. This poses another challenge since the bioavailability in the

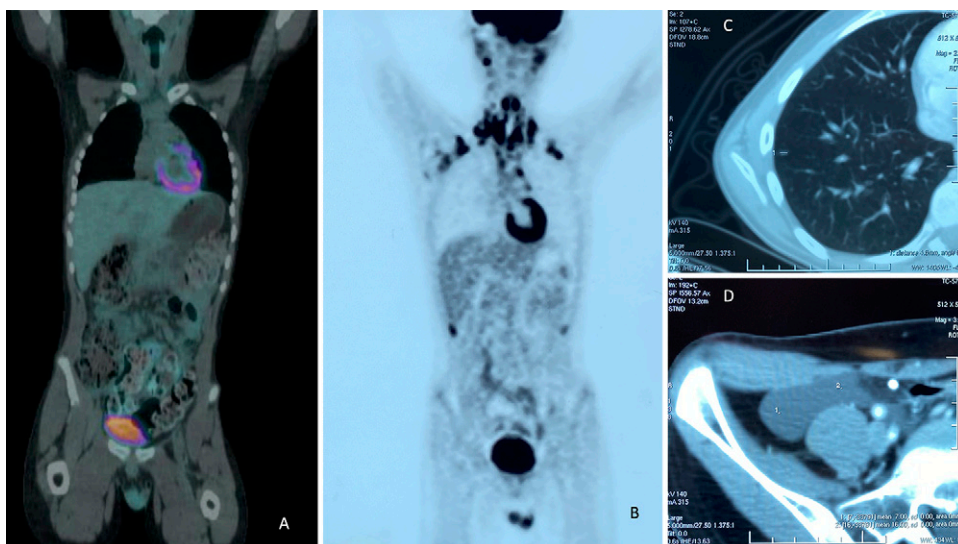


FIG. 4. PET CT scan showing cervical ganglia with metabolic uptake in compartments IIA and V bilaterally and another lymph node with uptake in cervical level VA, a mediastinal lymph node and three pseudonodular lesions in the right lung, compatible with metastatic activity.

TABLE 1. Cases of PBRMS with confirmed metastatic activity

Authors & Year	Age	Gender	Tumor Location	Resection	Metastasis	Adjuvant Therapy	Survival
Olson et al., 1985 ⁴	20 mos	F	Rt cerebellopontine angle	Subtotal	Pulmonary, mediastinal, splenic, & hepatic	Chemo & RT (not disclosed)	6 wks
Dropcho & Allen, 1987 ⁵	11 yrs	F	Interhemispheric, bilat frontal lobule + rt cerebellopontine angle	Subtotal	L1 vertebra	CBDA + RADIOTHERAPY (3600 + 1500 rad)	1 wk
Feitosa Pelajo et al., 2007 ⁶	7 yrs	F	Rt occipito-temporal	Total	Retroperitoneum, bladder, lungs, & cervical nodes	RT (dose not disclosed)	1 mo
Present case	14 yrs	M	Lt parieto-occipital lesion	Subtotal	Lungs, mediastinal, & cervical nodes	63 Gy, TMZ, CBDA	21 mos

CBDA = carboplatine; chemo = chemotherapy; CS = cerebrospinal axis; RT = radiotherapy; TMZ = temozolamide.

brain of said drugs is highly limited due to the blood brain barrier. Hence, the necessity for using different therapeutic strategies.

PBRMS is a rare tumor of the CNS that poses a diagnostic challenge but can be resolved with aid of immunohistochemical and genetic testing. Various therapies have been proven to effectively increase patient survival, although they have been anecdotally reported. More studies are needed to determine treatment's real efficacy.

Dedication

In loving memory of Paul Mondragón, whose love, laughter, joy, confidence, strength, and passion are dearly missed. You will always be a role model.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Mondragón-Soto, González-Soto. Acquisition of data: Mondragón-Soto, Del Valle. Analysis and interpretation of data: Mondragón-Soto, Del Valle. Drafting the article: Mondragón-Soto, González-Soto. Critically revising the article: Mondragón-Soto, Del Valle, de Leo-Vargas. Reviewed submitted version of manuscript:

Mondragón-Soto, González-Soto, de Leo-Vargas. Approved the final version of the manuscript on behalf of all authors: Mondragón-Soto. Administrative/technical/material support: Mondragón-Soto, de Leo-Vargas. Study supervision: de Leo-Vargas.

Supplemental Information

Previous Presentations

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