J Neurooncol (2008) 86:79–82
DOI 10.1007/s11060-007-9435-y

CLINICAL-PATIENT STUDIES

Successful treatment of a child with a primary intracranial rhabdomyosarcoma with chemotherapy and radiation therapy

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Received: 25 April 2007 / Accepted: 7 June 2007 / Published online: 20 June 2007
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Abstract Primary rhabdomyosarcoma of the central nervous system (CNS) is rare in both adults and children (Taratuto et al. (1985) Acta Neuropathol (Berl) 66(2): 98–104). The outcome in the majority of cases is poor, and many cases are associated with early mortality (Celli et al. (1998) J Neurooncol 36(3):259–267). There are very few cases reported in the literature of survival beyond 2 years after diagnosis. We report a case of primary intracranial embryonal rhabdomyosarcoma in a 5-year-old girl who was treated successfully with local radiation therapy (RT) and a combination of two different chemotherapeutic regimens. The patient is clinically well 26 months after diagnosis, with no definitive evidence of residual disease.

Keywords Brain tumor · Chemotherapy · Radiation therapy · Rhabdomyosarcoma · Surgery

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Introduction

Rhabdomyosarcoma is a soft tissue malignancy of skeletal muscle origin. It accounts for less than 5% of childhood cancers [1]. The most common primary sites are the head and neck, genitourinary tract, and the extremities. It is usually curable in children, with more than 70% of children presenting with localized disease surviving 5 years after diagnosis [2].

There are rare reports of primary rhabdomyosarcomas of the CNS occurring in both children and adults [3–8]. A review of the published literature identified only 38 previously reported cases [4]. These patients ranged in age from age 1 year to 68 years, the majority of which were children. The mean survival in these cases is 9.1 months. There have only been four previously reported cases of patients surviving longer than 24 months after diagnosis.

There is no definitive standard therapy for these tumors [4, 7]. Most cases are managed with surgical excision when possible, and many patients receive radiation therapy. In the review by Celli et al., 22 of the 38 patients previously reported received radiation therapy, with doses ranging from 25 Gy to 82 Gy [4].

There is no consensus regarding the role of chemotherapy, nor the best agents to administer if this modality is chosen [4]. Chemotherapy regimens with proven efficacy for extracranial rhabdomyosarcoma, as well as regimens with activity against intracranial tumors have been used.

We report the successful treatment of a child with completely resected intracranial embryonal rhabdomyosarcoma using adjuvant radiation therapy followed by vincristine, ifosfamide, carboplatin, etoposide (VICE) and vincristine, actinomycin, cyclophosphamide (VAC).

Ethics approval to report this case was obtained from the Clinical Research Ethics Board (CREB) of the University

of British Columbia. Consent was also obtained from the patient's parents. The authors have no financial conflicts of interest to report.

Case presentation

A 5-year-old female presented to the emergency department (ED) with a 2 day history of headaches. The headaches occurred at night and would persist until the morning, resolving later in the day. On the night she presented, she awoke suddenly with a severe headache and was inconsolable. She was developmentally normal prior to presentation.

Her initial neurologic examination revealed no localizing neurologic findings. Over the following hours in the ED her level of consciousness progressively decreased, and she eventually became obtunded. Her right pupil became sluggish then fixed.

Diagnosis

An emergent CT scan demonstrated a large acute hemorrhage in the right occipital lobe. There was evidence of mass effect, midline shift and herniation inferiorly through the tentorium (Fig. 1). The patient was immediately taken to the operating room where the hemorrhage was evacuated. A tumor in the same region was also identified, and was removed. A gross total resection was achieved. The lesion was intraparenchymal, with tumor present at the surface of the brain but with no attachment to the dura. Evidence of intratumoral hemorrhage was noted. The frozen section was that of a malignant neoplasm.

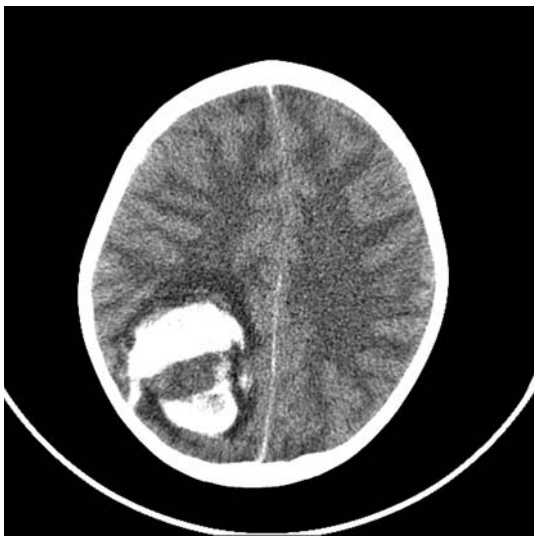

Fig. 1 The right occipital lesion on CT scan at presentation

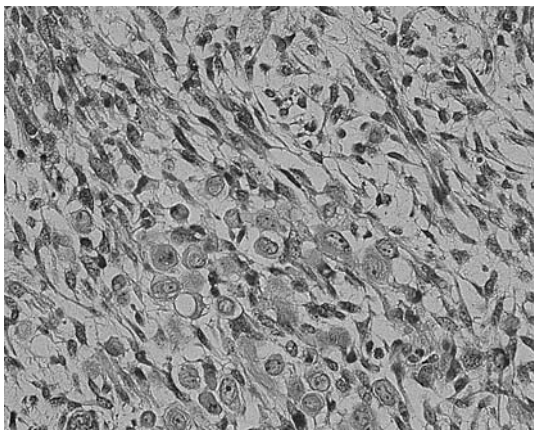

Fig. 2 Spindle cells in a myxoid background; oval and round rhadomyoblasts with vesicular nuclei and eosinophilic cytoplasm (H&E ×200)

The post-operative course was uneventful except for concerns about a left visual field defect post-craniotomy. The child was discharged home a few days later while the final pathology report was pending.

The tissue received for examination was pale gray in color and soft to firm in consistency. There were areas of hemorrhage in the tissue. Microscopic examination showed a spindle to round cell malignant tumor, which invaded the surface of the brain. The architectural pattern of the tumor varied from spindle cells in a myxoid background to more densely packed round cells with rhabdomyoblastic cytodifferentiation (Fig. 2). The rhabdomyoblasts were large cells with central irregular nuclei and dense eosinophilic cytoplasm (Fig. 3). Even in the more myxoid spindled areas scattered rhabdomyoblasts and more differentiated muscle cells were noted. A rare multinucleated giant cell was present. There were mitoses and scattered dying cells.

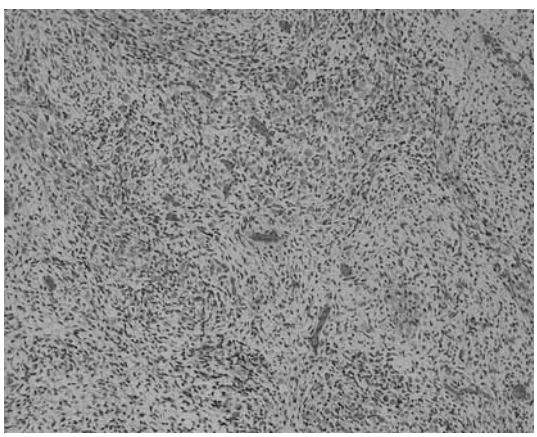

Fig. 3 Biphasic pattern of embryonal rhabdomyosarcoma; spindle cell areas alternating with areas in which the cells are round with vesicular nuclei and eosinophilic cytoplasm (H&E ×50)

No other elements such as bone, cartilage or fat were identified in the tumor.

Immunohistochemical stains demonstrated nuclear staining of the tumor cells for MyoD1 and myogenin. There was strong cytoplasmic staining of the tumor cells for desmin. The tumor cells were negative for neuron specific enolase, glial fibrillary acidic protein, S100 protein, synaptophysin, cytokeratin and epithelial membrane antigen.

RT-PCR for t(2;13) and t(1;13), t(X;18), t(11;22) and t(21;22) of alveolar rhabdomyosarcoma, synovial sarcoma and Ewing sarcoma/PNET respectively, were negative.

In summary, the pathological examination of the neoplasm showed gross, microscopic and immunohistochemical features of embryonal rhabdomyosarcoma. Upon histologic confirmation of the diagnosis, staging was performed to determine the primary source of the disease and the extent of spread. A Magnetic Resonance (MR) scan of her head and spine showed no evidence of disease. CT scans of her chest, abdomen and pelvis was normal, as was a total body MR scan. A bone scan revealed no abnormality. Her cerebral spinal fluid contained no tumor cells, nor did bilateral bone marrow aspirates and biopsies.

Therapy

The final diagnosis was a primary intracranial embryonal rhabdomyosarcoma with a gross total resection. She was treated with local three-dimensional (3D) conformal radiation therapy to a total dose of 4,500 cGy in 25 fractions. Adjuvant chemotherapy was administered. This included four courses of VICE (vincristine 1.5 mg/m^2, ifosfamide 1.8 g/m^2 daily for 5 days, carboplatin 400 mg/m^2/day daily for 2 days and etoposide 100 mg/m^2/day daily for 5 days) followed by 10 courses of VAC (vincristine, actinomycin-D and cyclophosphamide), given from weeks 12 through 39 as per the Children's Oncology Group protocol D9803 Regimen A. Following both the VICE and VAC chemotherapy G-CSF was given as a supportive care measure.

Complications included status epilepticus at the start of the second course of VICE, episodes of fever with neutropenia, thrombocytopenia, and reactions to platelet transfusions.

No neurologic problems were noted during therapy, and the aforementioned visual field defect resolved. Her personality was preserved, and there were no significant behavioural concerns.

Current status

The patient is alive and well 26 months after diagnosis. There have been no permanent neurologic sequelae, and she remains disease free. An area of rim enhancement persists at the margins of the resection cavity and has gradually decreased in size since completing therapy (Fig. 4).

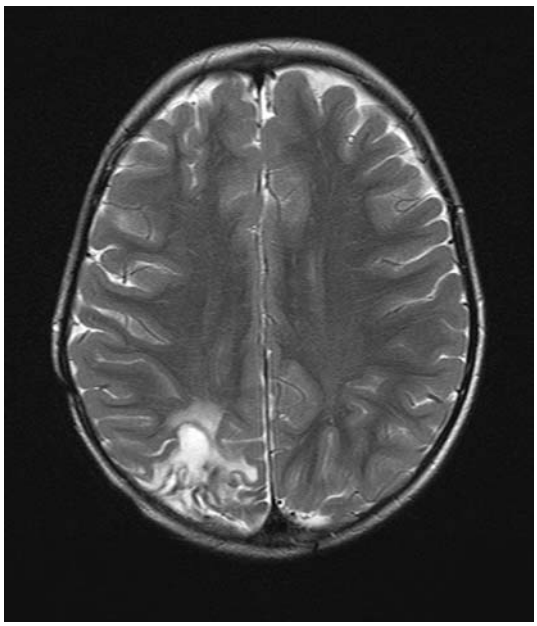

Fig. 4 The most recent MR imaging (axial, T2 weighted) at 25 months after diagnosis shows some nodular enhancement at the surgical bed which has gradually improved while off therapy. There is no definitive evidence of disease at this time

The child is now over 1 year post completion of treatment, asymptomatic and has no definitive radiologic evidence of disease at the present time. There have been no long-term effects of her treatment to date.

Discussion

Primary rhabdomyosarcomas of the brain are rare tumors, and less than 40 cases have been reported in the literature [4]. Most patients with these tumors die of their disease, often shortly after diagnosis. These tumors have specific histologic diagnostic criteria which are essential for accurate diagnosis [3, 4]. Distinction must be made from other CNS tumors, which contain muscle fibres [8]. Intratumoral hemorrhage has been described with rhabdomyosarcomas of brain and was noted at the time of surgery and confirmed microscopically in this case [7]. According to Tomei et al., the most common site for supratentorial lesions is in the frontotemporal region [7].

Rhabdomyosarcomas of the brain are known to recur rapidly after surgery [8]. The longest known survivor reported in the literature was 67 months post-diagnosis at the time of reporting. In addition to our patient, only four other cases have been reported to have survived beyond 24 months of diagnosis. All patients who have survived beyond 24 months, including the child described in this

report, underwent surgical resection (total or subtotal), and received both radiation therapy and chemotherapy with one exception. Matsukado et al. described a patient who survived a total of 26 months with surgery alone, but this child died with liver metastases [9].

The other three survivors received chemotherapy: one patient was given VAC and methotrexate [10], a second received VAC with cytarabine and methotrexate [11] and a third, who was alive after 30 months at the time of publication, received adjuvant RT (60 Gy), as well as cyclophosphamide, vincristine and actinomycin-D alternating with vincristine and carboplatin [4]. Due to the rarity of these tumors, no definitive recommendation regarding adjuvant therapy has been made.

We chose a therapeutic regimen similar to the latter case. After undergoing a gross total resection, the child described in the present case received 45 Gy of local conformal 3D RT in 25 fractions followed by adjuvant chemotherapy. There are no clear guidelines regarding the optimal dose of radiotherapy for such tumors in the CNS. While this type of tumor is known to be highly aggressive, higher doses of RT were considered inappropriate due to concerns about long-term neuropsychological sequelae. Extrapolation of data from studies of parameningeal rhabdomyosarcoma suggested that whole brain and craniospinal radiation therapy were not necessary when the risks of such interventions were considered [12]. In extracranial sites, the local recurrence risk after local radiation to this dose is expected to be less than 10% [13]. Vincristine, actinomycin-D and cyclophosphamide are widely accepted as the standard agents for rhabdomyosarcoma. In extracranial sites, localized embryonal rhabdomyosarcoma treated with complete resection, radiation and adjuvant VAC has been reported to be associated with a 5 year event free survival of 88% [2]. We postulated, based on the historical high recurrence risk of rhabdomyosarcoma in this location, that exposure to another active combination could be useful. Ifosfamide, carboplatin and etoposide are known to be effective in recurrent/ refractory childhood sarcomas including rhabdomyosarcoma [14]. These agents have also been used in CNS tumors [15].

Overall our patient tolerated the chemotherapy quite well, and aside from an episode of status epilepticus, she sustained no unexpected adverse events. As a result of prolonged suppression of her blood counts with delays in her chemotherapy, she required a 25% dose reduction of her cyclophosphamide over the last two courses of VAC. Her treatment was completed in 13 months.

Rhabdomyosarcoma of brain is a rare tumor, which is associated with a poor prognosis [3–8]. We describe here a girl diagnosed at the age of 5 years who remains in remission 26 months after surgical resection, with subsequent radiation therapy and adjuvant chemotherapy. No long-term effects of her treatment have been noted to date. We propose that consideration be given to this combination of therapy in other cases of this rare and often fatal type of CNS tumor.

References

1. Pizzo PA, Popplack DG (2006) Principles and practice of pediatric oncology, 5th edn. Lippincott Williams and Wilkins, Philadelphia, PA
2. Meza JL, Anderson J, Pappo AS, Meyer WH, Children's Oncology Group (2006) Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on intergroup rhabdomyosarcoma studies III and IV: the children's oncology group. J Clin Oncol 24(24):3844–3851
3. Taratuto AL, Molina HA, Diez B, Zuccaro G, Monges J (1985) Primary rhabdomyosarcoma of brain and cerebellum. Report of four cases in infants: an immunohistochemical study. Acta Neuropathol (Berl) 66(2):98–104
4. Celli P, Cervoni L, Maraglino C (1998) Primary rhabdomyosarcoma of the brain: observations on a case with clinical and radiological evidence of cure. J Neurooncol 36(3):259–267
5. Dropcho EJ, Allen JC (1987) Primary intracranial rhabdomyosarcoma: case report and review of the literature. J Neurooncol 5(2):139–150
6. Hayashi K, Ohtsuki Y, Ikehara I, Akagi T, Murakami M, Date I et al (1986) Primary rhabdomyosarcoma combined with chronic paragonimiasis in the cerebrum: a necropsy case and review of the literature. Acta Neuropathol (Berl) 72(2):170–177
7. Tomei G, Grimoldi N, Cappricci E, Sganzerla EP, Gaini SM, Villani R et al (1989) Primary intracranial rhabdomyosarcoma: report of two cases. Childs Nerv Syst 5(4):246–249
8. Yagishita S, Itoh Y, Chiba Y, Fujino H (1979) Primary rhabdomyosarcoma of the cerebrum. an ultrastructural study. Acta Neuropathol (Berl) 45(2):111–115
9. Matsukado Y, Yokota A, Marubayashi T (1975) Rhabdomyosarcoma of the brain. J Neurosurg 43(2):215–221
10. Shin KH, Whitehead VM (1980) Rhabdomyosarcoma of the brain. Can J Surg 23(6):576–578
11. Olson JJ, Menezes AH, Godersky JC, Lobosky JM, Hart M (1985) Primary intracranial rhabdomyosarcoma. Neurosurgery 17(1):25–34
12. Michalski JM, Meza J, Breneman JC, Wolden SL, Laurie F, Jodoin M et al (2004) Influence of radiation therapy parameters on outcome in children treated with radiation therapy for localized parameningeal rhabdomyosarcoma in intergroup rhabdomyosarcoma study group trials II through IV. Int J Radiat Oncol Biol Phys 59(4):1027–1038
13. Regine WF, Fontanesi J, Kumar P, Ayers D, Bowman LC, Pappo AS et al (1995) Local tumor control in rhabdomyosarcoma following low-dose irradiation: Comparison of group II and select group III patients. Int J Radiat Oncol Biol Phys 31(3):485–491
14. Van Winkle P, Angiolillo A, Krailo M, Cheung YK, Anderson B, Davenport V et al (2005) Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the children's cancer group (CCG) experience. Pediatr Blood Cancer 44(4):338–347
15. Lopez-Aguilar E, Sepulveda-Vildosola AC, Rivera-Marquez H, Cerecedo-Diaz F, Hernandez-Contreras I, Ramon-Garcia G et al (2000) Preirradiation ifosfamide, carboplatin, and etoposide for the treatment of anaplastic astrocytomas and glioblastoma multiforme: a phase II study. Arch Med Res 31(2):186–190