A successful case of an anaplastic meningioma treated with chemotherapy for soft tissue sarcomas

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Practice points

- Malignant meningioma has a bad prognosis in pediatric and adult patients.
- Chemotherapy does not have an established role like therapeutic options.
- Ifosfamide and doxorubicin are active drugs in sarcoma and sarcoma-like tumors.
- An integrated multidisciplinary approach could lead to a better outcome.
- In this case, proposed treatment has improved disease-free survival and overall survival, despite the rapid postoperative recurrence.

Malignant meningioma has a bad prognosis. Surgery and radiotherapy are the most effective therapeutic options, without an established role for chemotherapy. We report a case of 2-year-old male child with diagnosis of postoperative relapse of a malignant meningioma. Considering the rapid progression, the young age and the lack of effective therapeutic alternatives, the patient underwent multidisciplinary anticancer treatment with a protocol made for soft tissue sarcomas (EpSSG NRSSTS 2005 protocol), with positive outcome. This case represents a successful management of an anaplastic meningioma with a multimodal treatment, including chemotherapy, in a pediatric patient.

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Background

Childhood meningiomas are uncommon lesions. Meningiomas occur mostly in middle-aged or elderly patients, but they can also occur in younger patients, especially in those with genetic syndromes such as neurofibromatosis type 2 (NF2) [1–3].

There are many histological subtypes of meningioma, which differ in their level of malignancy. The WHO classifies meningiomas in three grades: I, classical; II, atypical; and III, anaplastic/malignant [4]. Malignant meningiomas (WHO grade III) are the rarest, but aggressive type of meningiomas and they include papillary, rhabdoid and anaplastic histological subtypes. Although considered malignant, cases reporting distant metastases are really isolated, even if they can locally recur. Anaplastic meningiomas are understudied compared with other subtypes for the low incidence [4].

KEYWORDS

- anaplastic meningioma
- chemotherapy • pediatric solid tumors

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Children have higher recurrence rates than adults and decreased overall survival [1,5]. Failing clear statistically validated guidelines, therapeutic approaches for child and adolescent meningiomas have been extrapolated from literature reports and protocols used for adult meningiomas. The gold standard therapy for malignant meningioma is complete surgical resection of the lesion. However, surgery alone is typically insufficient, due to the high local recurrence rate, and the surgical debulking does not guarantee a good outcome. Radiotherapy remains controversial in younger patients for the risk of significant late sequelae. This is particularly important in infants and young children whose CNS is more vulnerable to the effects of radiotherapy [6,7].

Chemotherapy is not often used for adult meningiomas. Current guidelines recommend only few drugs that can be used to treat patients with refractory and high-grade meningiomas: hydroxyurea, IFN- α 2B and sandostatin long-acting release [8].

For pediatric patients, there is no standardized systemic therapy, but chemotherapy may have a role in anaplastic tumors [5,9].

We reported a young patient with anaplastic meningioma successfully treated with a chemotherapy combined to conventional radiotherapy.

Case presentation

In November 2011, a 2-year-old male child was admitted to our Hospital for a motor deficit of the left arm and an ipsilateral cranial nerve VII palsy. Physical examination confirmed neurological involvement with other signs like motor deficit of lower left limb and mild drowsiness with headache. A brain MRI scan evidenced a hydrocephalus due to a giant tumor ($67 \times 61 \times 60$ mm) of the right hemisphere (**Figure 1 & Figure 2A**). The lesion had polylobate margins and global inhomogeneous signal. There were also perilesional edema and mass effect on ventricular system and brainstem. He initially underwent an endoscopic third ventriculostomy with septostomy to treat hydrocephalus. After 4 days, a radical resection of the lesion was performed. After right fronto-temporal craniotomy, the tumor was resected

Figure 1. MRI performed at diagnosis. (A) Coronal T1 sequence with contrast; **(B)** sagittal T1 sequence with contrast; **(C)** axial T2 sequence (arrows indicate the arachnoid plane of lateral sulcus with tumor adhesion).

Figure 2. MRI scans of the anaplastic meningioma. All pictures are of MRI in T1 sequence with contrast ([i] coronal; [ii] sagittal). (A) Images are related to diagnosis, (B) first postoperative control, after 48 h, and last follow-up, (C) 54 months after diagnosis.

with ultrasonic tissue ablation system for central portion and with classical dissection along the cleavage plane. It appeared encapsulated, hard, with slightly bleeding and extra-axial growing.

Postoperative computed tomography and MRI did not show persistent disease (Figure 2B).

About pathological evaluation, the tumor was mainly composed of a proliferation of atypical elongated sarcoma/melanoma-like cells with prominent nucleoli (Figure 3A). In some areas, the neoplastic cells showed marked pleomorphism and multinucleation (Figure 3B). The interstitial space contained collagen bundles. There were occasional psammoma bodies and rare whorls. Multiple areas of necrosis were present (Figure 3C). Hemorrhage and numerous blood vessels with dilated lumina and thin wall were evident particularly at the periphery of the tumor. Brain invasion was observed (Figure 3D). There were up to seven to eight mitoses for ten high power fields (HPFs) (Figure 3E & F). The proliferative index, determined by estimating the percentage of the Mib-1 immunopositive neoplastic cells in the total tumoral cells in the most positive areas was 20%. Based on these features and, in particular, considering the obviously malignant cytology,

the tumor was best classified as an anaplastic meningioma (WHO grade III).

Diagnosis was confirmed by the review of the CNS national panel of pathologists. Cerebrospinal fluid (CSF) obtained via lumbar puncture was performed. CSF cytology was positive.

After 1 month, a Gd-enhanced brain MRI showed a relapse on surgical margins. Considering the rapid progression, the young age and the lack effective of standardized therapeutic alternatives, he was started on a therapeutic program according to international soft tissue sarcomas protocol (EpSSG NRSSTS 2005 protocol – Non-RabdomyoSarcoma Soft Tissue Sarcomas 2005 protocol).

The protocol provides both chemotherapy and radiotherapy, with an initial phase of induction chemotherapy (three cycles of ifosfamide 3 g/m²/day for 3 days plus doxorubicin 37.5 mg/m²/day for 2 days every 21 days) followed by concomitant chemoradiotherapy (with only ifosfamide at the same dose and timing) and a final cycle of consolidation chemotherapy. Patient received focal radiotherapy for a total dose of 54 Gy in 1.8-Gy daily fractions on clinical target volume. The clinical target volume was obtained

Figure 3. Histological features. (A) Sarcoma/melanoma-like cells with prominent nucleoli; (B) multinucleation; and (C) necrosis. Hematoxylin and eosin; original magnification (A–B) 20×, (C) 10 X; (D) brain invasion; (E–F) mitoses (arrows). Hematoxylin and eosin; original magnification (D) 20×, (E–F) 40×.

by adding 1 cm to the gross tumor volume. The gross tumor volume was defined on postoperative contrast-enhanced T1-weighted MRI and included the surgical cavity. Overall treatment was applied from December 2011 to April 2012; it was well-tolerated, even if a dose reduction of doxorubicin was required for hematological toxicity (50% of the starting dose at the last two cycles).

At the end of treatment, an MRI showed stable disease and CSF cytology was negative. The child started follow-up with surveillance MRIs.

The patient is alive without evidence of recurrent disease 54 months after starting chemotherapy (Figure 2C). At the moment he is 6 years old, and his physical and cognitive development is normal. However, neurological disorders (deficit of left seventh cranial nerve, and motor deficits of the upper and lower left limbs) persist. Cardiac or endocrine disorders, as late side-effects of the therapy, are not documented. He maintains a Lansky Performance Score >90.

Discussion & conclusion

Meningiomas and even more the high-grade meningiomas are rare in pediatric population [10]. Gold standard treatment of a meningioma is surgery. Surgical resection allows definitive diagnosis, reduces mass effect and alleviates signs and symptoms. Excision should be as complete as possible to allow a possible cure. If possible, a margin of dura should be excised around the tumor. If bone is involved, it must be completely resected too [9].

After surgery, another key role is played by radiotherapy. Anaplastic meningioma should be treated by conventional fractionated radiation therapy, after resection [9]. No conventional role for chemotherapy currently exists: several drugs or combination have been tested, but none of these have shown convincing effect on atypical or anaplastic meningiomas. The main tested drugs are mifepristone (an antiprogesterone agent) [11], IFN- α -2B [12], long-acting somatostatin analog [13] and hydroxyurea [14].

In a limited number of primary malignant meningiomas treated with adjuvant external radiotherapy and cyclophosphamide plus adriamycin, and vincristine, chemotherapy seemed to improve median survival when compared with exclusive surgery and was associated with acceptable toxicity [5].

Currently, the main topics of research in meningioma are anti-PDGF and anti-EGF compounds (Phase II studies) [9].

We described a child, who initially underwent complete surgery, but after 1 month an MRI scan showed a local recurrence, and CSF was positive for tumor cells. Therefore, the child was subjected to a chemotherapy plus radiotherapy program. Considering the malignancy of the tumor, we needed an active systemic treatment in association with local radiotherapy. He was subjected to the EpSSG NRSSTS 2005 protocol (ifosfamide and doxorubicin) for soft tissue sarcomas, which provides the integration of radiotherapy with concomitant chemotherapy.

Anaplastic meningiomas are similar to soft tissue sarcoma as they exhibit local aggressiveness and the propensity to spread by CSF correlates with histologic grade similar to the propensity for distant metastasis in sarcomas.

About follow-up, close imaging should be recommended given the high recurrence rate in anaplastic meningiomas (WHO grade III). The 3 years progression-free survival rate ranges from 0 to 8.7% [15,16]. Although radiotherapy and chemotherapy are considered as significant risk factors for secondary cancer, current findings do not support radiotherapy or chemotherapy withdrawal based on risk of future second tumors, since recent publications reported about a quite low rate of second brain cancer in patients treated with radiochemotherapy (0.08–1.25%) [17,18].

This successful case (over 3 years of disease-free survival, without relapse) represents an interesting contribution, with strong rationale, to propose research protocols with multimodal therapy including radiotherapy and chemotherapy in anaplastic meningioma, especially in pediatric cases.

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Informed consent disclosure

Clinical activity described in this report has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The authors state that they have obtained verbal and written informed consent from the relevant parent(s)/guardian(s) for the inclusion of their child's medical and treatment history within this case report.

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