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Childhood's gliosarcomas: pathological and therapeutical considerations on three cases and critical review of the literature

Received: 14 December 2004
Published online: 16 March 2006
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Abstract *Background:* Gliosarcoma is a rare cerebral tumor that has only recently been classified as a separate clinico-pathological entity, even though it remains closely related to glioblastoma in terms of both its clinical and therapeutic characteristics. The onset of this tumor during childhood is particularly unusual.

Discussion: The authors describe three cases of gliosarcoma in three patients of 13, 15, and 16 years old, in an attempt to identify any distinctive aspects of the "juvenile" variety. On the basis of their personal experience and in the light of the available literature, the authors review the salient features of this pathological condition in young patients to identify any distinctive aspects as well as to define

the significance of the extent of the sarcomatous component and of a "meningioma-like" appearance of the lesion, in terms of survival.

Conclusion: In particular, they emphasize how modern diagnostic-therapeutic protocols make it possible to achieve a massive cytoreduction of the lesion in absolute safety in many cases, while avoiding further deficits in others, thus ensuring not only significant survival times but also a good quality of life.

Keywords Gliosarcoma · Glioblastoma multiforme · MRI · Surgery · Chemotherapy · Radiotherapy

Introduction

Gliosarcoma is a rare cerebral tumor, closely related to glioblastoma, whose histopathological features display a biphasic component made up of clear gliomatous areas and others with a frank sarcoma-like appearance [1, 3, 4, 12, 18, 26].

Described for the first time by Stroebe in 1895 [31], for a long time this lesion was considered a hybrid of other central nervous system tumors.

Like glioblastomas, gliosarcomas are highly malignant tumors which correspond histologically to grade IV according to the most recent WHO classification [21].

The clinical and prognostic features of three cases of gliosarcoma in childhood (one of which was probably radio-induced) are discussed in the light of the available literature in an attempt to identify any distinctive aspects of the "juvenile" variety.

Case 1

A 15-year-old girl who presented a 10-day history of circadian headache associated with morning vomiting, often not preceded by nausea. Two days before admission, she had suffered a bout of loss of consciousness lasting about 10 min followed by a state of confusion. Neurological examination revealed a syndrome from endocranial hypertension with papilledema at fundus oculi examination (KPS = 60).

Brain magnetic resonance imaging (MRI) with i.v. contrast soministration documented an expansive lesion in a right temporal site with the characteristics of a high-grade glioma (Fig. 1). At surgery, "en bloc" removal of a large greyish-yellow lesion with a hard-elastic consistency was achieved: the lesion had a maximum diameter of about 4 cm and adhered to the dura mater. Postoperative MRI

(within 24 h of operation) confirmed macroscopically total removal of the lesion.

Histopathological examination showed a tumor resembling glioblastoma, but with an extensive sarcomatous-like component containing spindle-cell elements, either grouped in bundles or without a clear architectural layout. This aspect was observed in more than half the histological sections (at least five) harvested from different areas of the tumor after “en bloc” removal, and was found to be highly positive for reticulin. MIB-1 was 35%.

Postoperative recovery was normal and the patient was discharged on day 4 in excellent general and neurological conditions (KPS = 100; N.E. negative).

The girl’s parents refused the neoadjuvant procedures proposed (chemotherapy and radiotherapy). After living a normal life for 4 months, the patient presented two episodes resembling “generalized comitial seizures”: subsequently, over the next few days, there was a progressive impairment of consciousness until she became comatose. No specific medical treatment was administered apart from support therapy with steroids (betametasone 4 mg twice a day i.m.), antiepileptic medication (phenobarbital 100 mg. i.m. in the evening) and gastric protection (ranitidina fl e.v., three times a day). No further radiological investigations were performed and the patient died 1 month after the onset of these new symptoms.

Case 2

The second case is that of a 13-year-old girl. A few days before admission, she had begun to suffer from severe headache and psychomotor slowing: she became comatose a few hours before admission. Computed tomography (CT)-scan and MRI with contrast enhancement documented

a large midline tumor in a bilateral parieto-occipital site, reaching as far as the splenium of the corpus callosum (Fig. 2). Neurological assessment showed a comatose state with a finalistic response to painful stimuli and anisocoria right > left.

Emergency surgery was performed and the lesion was removed subtotally: the red-greyish lesion was easily aspirated. Early postoperative MRI (2 days after treatment) confirmed the extent of removal. The first two postoperative days were spent in our intensive care unit. After another 10 days, she was discharged in excellent general and neurological conditions (neurological examination negative; KPS = 100).

Histological examination showed a prevalent population with the features of glioblastoma and a minor “sarcoma-like” component involving less than 25% of the histological sections/samples examined (five in total from different areas of the lesion). The MIB-1 index was 40%.

Treatment was begun with conformational radiotherapy using the multileaf method with linear accelerator (LINAC) (total 64 Gy) associated with concomitant chemotherapy using temozolomide (75 mg/m² pro die on the days scheduled for radiotherapy): this was followed by 12 sequential cycles in concordance with the classic protocol for administration of this drug (200 mg/m² for 5 days every 28 days).

Nine months after surgery, the patient is in good conditions and does not present signs of recurrence.

Case 3

The third case is that of a 16-year-old boy. Ten years earlier, he had been irradiated in another country for an angioma of the scalp: a total of 25 Gy had been delivered, using a

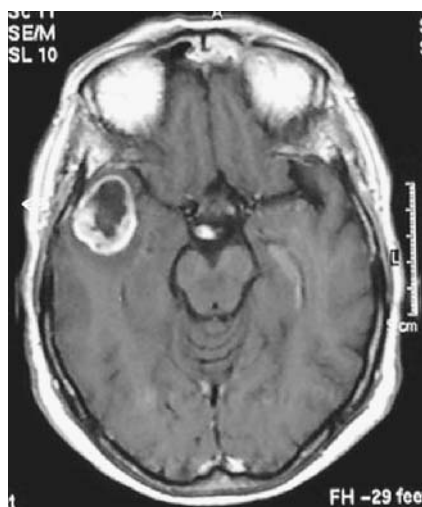


Fig. 1 Case 1. MRI showing a roundish neoplasm in the right, temporal site enhancing disomogeneously after contrast administration



Fig. 2 Case 2. MRI showing a large midline neoplasm in the bilateral parieto-occipital site, reaching as far as the splenium of the corpus callosum, with peripheral contrast enhancement

method apparently still under development. Two months before admission, he started to suffer from repeated paresthesia-like episodes (transient loss of sensibility) on one side of his body (right limbs): these attacks lasted a few minutes each and occurred several times a day.

The onset of a mild hemiparesis of the right limbs prompted an MRI brain scan which was integrated by a spectroscopic and functional study. A left parasagittal frontal tumor slightly involving the main motor area was visualized (Fig. 3a,b). The lesion appeared to originate from the meninges of the left frontal convexity and presented the characteristics of a meningioma, even though spectroscopic examination showed high NAA/Cho ratios for a benign meningeal lesion.

At operation, the lesion appeared reddish and bleeding. Its consistency was soft but it adhered tightly to the dura

mater and presented a clear plane of cleavage with the surrounding brain tissue. An “en bloc” removal was performed, as confirmed by early postoperative MRI. Histopathological examination of the five sections taken showed the presence of a clear population with the characteristics of glioblastoma (GFAP positive), associated with a second, reticulin-positive area with sarcoma-like features (Fig. 3c,d). The MIB-1 index was 40%. The second component was observed in more than half of the sections examined.

Postoperative recovery was uneventful and the patient was discharged in excellent general and neurological conditions (neurological examination negative; KPS = 100).

Integrated treatment consisting of conformational radiotherapy using the multileaf technique for a total of 64 Gy to the surgical field, plus chemotherapy with temozolomide

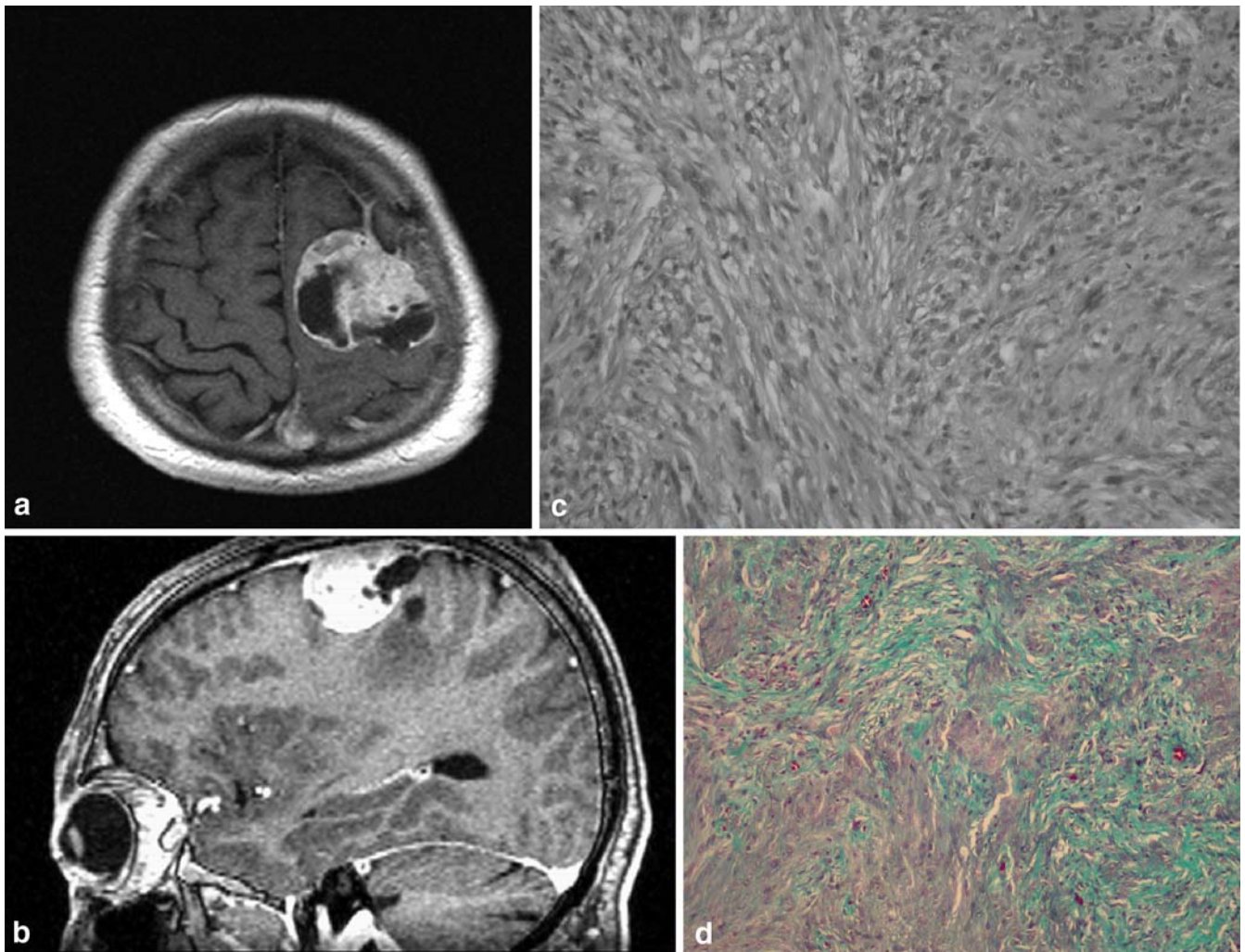


Fig. 3 Case 3. **a,b** MRI showing a roundish neof ormation in the left, frontal site with contrast enhancement and areas of hypointensity on T2-weighted sequences within it. The tumor seems to originate from the dura mater and extend into the brain parenchyma in the close vicinity of the premotor area. **c,d** Histology. **c** H&E stain

×400. The tumor appears to have an architecture organized principally in layers. In particular, cellular polymorphism and mitosis are evident. **d** Reticulinic coloration shows an intense, widespread positivity

(75 mg/m² for the duration of radiotherapy) was performed. This was followed by 12 cycles of chemotherapy with temozolomide (200 mg/m² for 5 days every 28 days).

Two years after operation there are no signs of disease progression.

Discussion

Gliosarcoma is a rare glial tumor which accounts for 1.8–8% of glioblastomas [7, 15, 17, 24] with an estimated annual incidence in Europe and the USA of one case per million inhabitants [14]. Gliosarcomas generally appear in the brains of adult patients. The most frequent localization seems to be the temporal lobe followed by the parietal and frontal lobes [7]. There is a peak incidence between 40 and 60 years of age [21].

In their series, Meis et al. [17] and Galanis et al. [7] describe an even higher age-related localization (more than 50% of patients aged over 60). Reports of cerebral gliosarcoma in young patients are very rare [6, 8, 11, 13, 22, 23, 27].

Okami et al. [22] found just eight cases of gliosarcoma in children published in the literature, to which we can add the radio-induced one described by Malde et al. [16], the three described by Sarkar et al. [32], and the three described in this study.

Gliosarcomas may metastasize to the lung, the pleura, the lymph-nodes, the bone marrow, the liver, and the spinal cord, with a higher frequency than glioblastoma [5, 25, 33]. Maiuri et al. [15] refer to an incidence of extracranial metastases ranging from 15–30% of the total number of patients. The histogenetic origin of the double population observed in gliosarcomas is an extremely controversial issue. Recent genetic studies have corroborated the theory of a monoclonal origin of gliosarcoma, the sarcomatous component deriving from neoplastic glial cells that have assumed the phenotype of sarcomatous cells during tumor progression [3, 4, 12, 18, 26]. Moreover, the glial cells and the cells with a sarcomatous appearance within the same tumor share the same genetic aberrations [1, 3, 4, 18, 26]. In fact, Biernat et al. [3] demonstrated an identical p53 mutation in the two tumor areas. Homozygous p16 deletion, PTEN mutation, and coamplification of MDM2 and CDK4 are other gene alterations detected in both the gliomatous and sarcomatous components of gliosarcoma [24, 28, 29, 31]. These findings were confirmed by the studies reported by Actor et al. [1] demonstrating the close similarities in the genomic changes that occur in gliosarcomas and glioblastomas. It seems likely that gliosarcoma possesses a higher genic stability. The expression of the sarcomatous phenotype could be related to gain-amplification of the genes of proximal 12q [1].

In gliosarcomas, as in gliomas, the possibility of radio-induction of the tumor has been demonstrated [30, 32]. The criteria for defining a radio-induced tumor are the traditional ones described by Cahan et al. established in 1948 and modified in 1972 by Schrantz, namely: (1) the tumor must appear in the irradiated area; (2) no tumor was present before (or at the time of) radiation therapy; (3) there must be an adequate latency period between irradiation and the appearance of the tumor; (4) the radiation-induced tumor must have a different histology from the one treated by radiotherapy; and (5) there must not be any predisposing conditions such as neurofibromatosis, xeroderma pigment, etc.

Gliosarcomas are mainly described after irradiation for pituitary adenoma or extracranial lesions such as leukemias or lymphomas [20]. Our case 3 had been treated for a cutaneous angioma 10 years previously: to our knowledge, this is the first case described following radiation for this condition.

The diagnosis of gliosarcoma was founded on the histopathological criteria defined by Meis in 1990 [18]: (1) the tumor must be bimorphic, namely composed of two malignant but morphologically distinct cell populations; (2) one of the two components must have an astrocytic nature with areas of necrosis, in accordance with the criteria adopted for defining glioblastomas; (3) the sarcomatous component must resemble a spindle-cell sarcoma; and (4) a minimum of one confluent, sarcomatous area must fill one medium power field (10× objective with 10× eyepiece). Moreover, immunohistochemistry for glial fibrillary acidic protein (GFAP) and reticulin stain was performed to distinguish the glial from the sarcomatous component of the neoplasia. In one case, in addition to glial and sarcomatous elements, there was also cartilaginous and osteoid tissue [2, 9, 10].

CT findings are variable with features that mimic a variety of tumors ranging from meningioma to malignant glioma. In the former, the use of modern diagnostic imaging techniques such as resonance spectroscopy could probably improve preoperative diagnostic accuracy. Moreover, this variant, the so-called meningioma-like gliosarcoma, does not appear to have been previously described in children, making our case the first meningioma-like gliosarcoma in childhood, owing to the fact that resonance spectroscopy documented features similar to those of a lesion originating from the meninges (Fig. 3).

Average survival after diagnosis of gliosarcoma is less than 1 year [7, 18], ranging from 6 to 14.8 months with occasional long survivors to more than 6 years. Prognosis seems to be slightly better for lesions with a prevalent sarcomatous component and with radiological and surgical features resembling meningioma [15, 24]. In our case 3, in fact, these features were present and the tumor could not be distinguished from a meningioma: although only 2 years have passed since operation, the clinical evolution of the

lesion seems to confirm that a slower growing subtype does exist.

In childhood, however, although very few cases have been described, long survival times after initial diagnosis have been observed (21 ms, Radkowski et al. [27]; 34 ms, Ono et al. [23]; 24 ms, our case 3). In our opinion, owing to the similarity between gliosarcoma and glioblastoma, treatment should be the same for both histotypes.

The first therapeutic step is surgical cytoreduction of the lesion with the aid of the functional and morphological imaging techniques available today (functional and spectroscopic MR; intraoperative neuronavigation with functional mapping) as well as microsurgical techniques and ultrasonic aspirator.

An early postoperative MRI control investigation (within 24 h of surgery to avoid the artifacts that may occur soon after operation) is useful for assessing the extent of removal together with a spectroscopic study of the bordering areas to rule out the presence of any suspicious pathological tissue.

In general, surgery requires a few days of hospitalization (two to four): it is followed 20 to 40 days later by radiation treatment with conformational techniques for a total of about 60 Gy delivered to the surgical bed and as far as 2 cm outside the borders of the lesion on T1 sequences, using LINAC.

The dosages of radiotherapy delivered differ in the literature (from 40 to more than 60 Gy, even hyperfractionated). However, we believe that doses lower than 60 Gy are not sufficient to guarantee an efficacious local treatment of the residual glioma.

Chemotherapy with temozolomide, in view of the glial origin of the lesion, may represent the third step of

treatment. In our cases 2 and 3, this therapeutic protocol was applied. In the literature, only Morantz et al. [19] comment on the efficacy of chemotherapy in terms of tumor evolution, describing a slight improvement of survival (36 vs 33 weeks).

In our opinion, the use of temozolomide is justified because not only is it easy to administer and is well-tolerated but its effectiveness, although moderate and variable, is equal to that of other chemotherapeutic protocols (even those employing more than one agent) which are decidedly more toxic and more difficult to administer: last but not the least, no hospitalization is necessary, not even in day-hospital.

Conclusion

Our current knowledge of gliosarcoma coupled with recent technological innovation (neuronavigation, functional and spectroscopic MRI, intraoperative brain mapping), make it possible to establish a rational diagnostic and therapeutic approach to this lesion while keeping the risks associated with a brusque cytoreduction to a minimum. In fact, it is mandatory to consider the outcome of treatment in terms of quality of life, especially in this age group of patients.

The evidence indicating that the extent of the sarcomatous component and a "meningioma-like" radiological appearance of the lesion are predictive of a better response to treatment, are findings of pathological interest in adults. Although very little data is available, it does seem to confirm this finding.

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