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CLINICAL–PATIENT STUDIES

Radical surgery after chemotherapy: a new therapeutic strategy to envision in grade II glioma

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Abstract While surgery is proned in low-grade glioma (LGG), the invasion of functional areas frequently prevents a complete resection. We report the first case of a patient operated on for a left frontal LGG, diagnosed because of seizures, with partial resection due to an invasion of the controlateral hemisphere. Chemotherapy enabled a regression of this controlateral extension. Postchemotherapy surgery performed with intraoperative functional mapping then allowed a complete resection, without sequelae. The patient has a normal socio-professional life, with no seizure. No other treatment was given. There was no recurrence, with a follow-up of 2 years since the second surgery (3.5 years since the first symptom). We propose a new therapeutic strategy in unresectable LGG, with preoperative chemotherapy, to make a radical surgery possible in a second step, while preserving the quality of life.

Keywords Low-grade glioma · Chemotherapy · Surgery · Brain mapping

While still controversial, resective surgery of WHO grade II glioma (LGG) seems to have an actual impact on the natural history of the tumor, essentially when the resection is total on the control MRI [1, 2]. However, due to the frequent location of LGG within eloquent areas [3], and its infiltrative nature, complete surgical removal is often impossible. In case of ‘‘unresectable’’ LGG, because of the risk of growth, migration and anaplastic transformation [4], once the histological diagnosis is affirmed by a biopsy, the classical attitude is to perform radiotherapy [5] or more recently, to propose initial chemotherapy [6]. Indeed, a decrease of the volume of LGG was reported using Temozolomide (TMZ), with preservation or even improvement of the quality of life [7–9]. Interestingly, it could be hypothesized that such a regression of the invasion of the peritumoral eloquent brain areas, induced by chemotherapy, might make a complete surgical resection of the residual glioma possible, even though it appears impossible before the chemotherapy. Nevertheless, to our knowledge, there is currently no report in the literature, which has proposed to perform a radical surgery of LGG in adults, after a tumoral regression under chemotherapy.

Here, we describe for the first time the case of a patient harboring a LGG located within the left frontal lobe, and invading the controlateral hemisphere through the corpus callosum—thus preventing to perform a radical resection during a first surgery. As a consequence, because of a progression of the residue on sequential MRIs, chemotherapy was given. Due to a regression of the controlateral invasion, a surgery was decided following 8 cycles of TMZ, and allowed a complete removal of the residual tumor. Since the diagnosis of LGG was confirmed by the second histological examination, and since the resection was total, no other complementary treatment was given. With 2 years of follow-up, the patient continues to have a normal life, with no recurrence on the control MRIs.

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On the basis of this case report, we propose a new therapeutic strategy in unresectable LGG, with preoperative chemotherapy in order to reduce the tumoral infiltration, thus to improve the surgical resectability.

Case report

Patient

A 40-year-old right-handed man, with no history of neurological disease, presented a first seizure in August 2002. An MRI showed the existence of a lesion involving the left frontal lobe, especially the mesial structures, with an invasion of the corpus callosum. A surgery was performed 1 month later in another institution, under general anesthesia (without functional mapping), and was termined prematurely with a partial resection (Fig. 1). The histological examination made the diagnosis of grade II oligodendroglioma, with no sign of anaplasia. As a consequence, no complementary treatment was given, and the patient returned to a normal life.

Chemotherapy

During the follow-up, sequential MRIs showed a progression of the glioma invasion, especially to the right hemisphere via the corpus callosum (Fig. 2a). At this moment, the patient was referred in our department. Due to the controlateral extension (more than 2 cm from the midline to the right side), the glioma was considered as unresectable. However, taking account of the glioma growth and migration, chemotherapy was decided. Between July 2003 and February 2004, 8 cycles of TMZ were administered orally—from day 1 through 5 at a starting dose of 200 mg/m^2. The patient continued to lead a normal life under chemotherapy. Moreover, on control MRIs, a complete disappearance of the right hemispheric infiltration and a partial regression of the callosal invasion were observed (Fig. 2b). However, despite this initial shrink, the residual tumor stopped to regress after the sixth cycle of TMZ. Since the glioma was now accessible to a surgical resection, a second operation was performed in March 2004.

Surgery

Because of the location of the tumor near eloquent regions, i.e. motor areas (precentral LGG) and language areas (glioma within the dominant hemisphere), the second surgery was performed on awake patient, with intraoperative functional mapping using cortico-subcortical electrostimulations [10]. Thus, the resection was continued until the functional structures were encountered, in order to optimize the quality of tumor removal while minimizing the risk of postoperative sequelae [2]. In particular, the inferior fronto-occipital fasciculus, involved in semantic processing, generated semantic paraphasia in the postero-lateral part of the cavity, and constituted the deep limit of the resection [11]. On the midline, the genu of the corpus callosum was removed, but it was decided to not continue the resection in the right hemisphere, due to the shrink of the tumor at this level following TMZ.

Postoperative course and follow-up

The postsurgical course was uneventful, except transient language disorders which were completely resolved following 2 months of speech rehabilitation. The histological examination confirmed the diagnosis of grade II oligodendroglioma, with no sign of anaplasia. The Ki 67 was less than 3%. Interestingly, a sample collected within the junction of the right

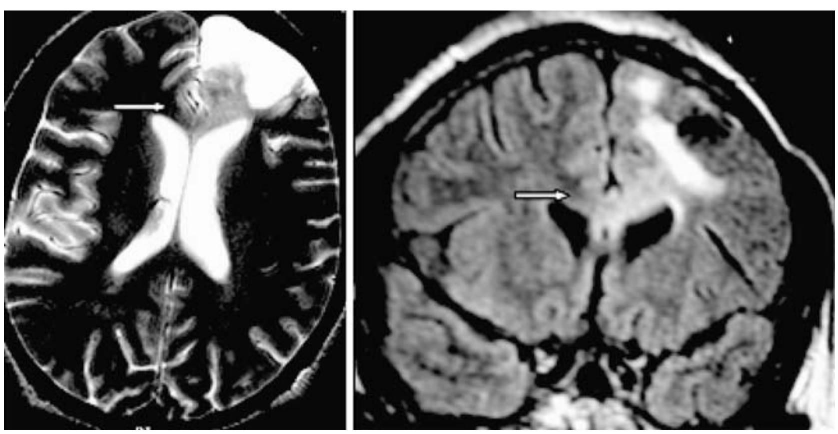

Fig. 1 Axial T2-weighted MRI and coronal FLAIR-weighted MRI, after the first surgery, showing a left LGG involving the fronto-mesial structures, uncompletely removed (posterior residue invading the left side of the corpus callosum). At this time, there was no controlateral extension of the tumor (arrows)

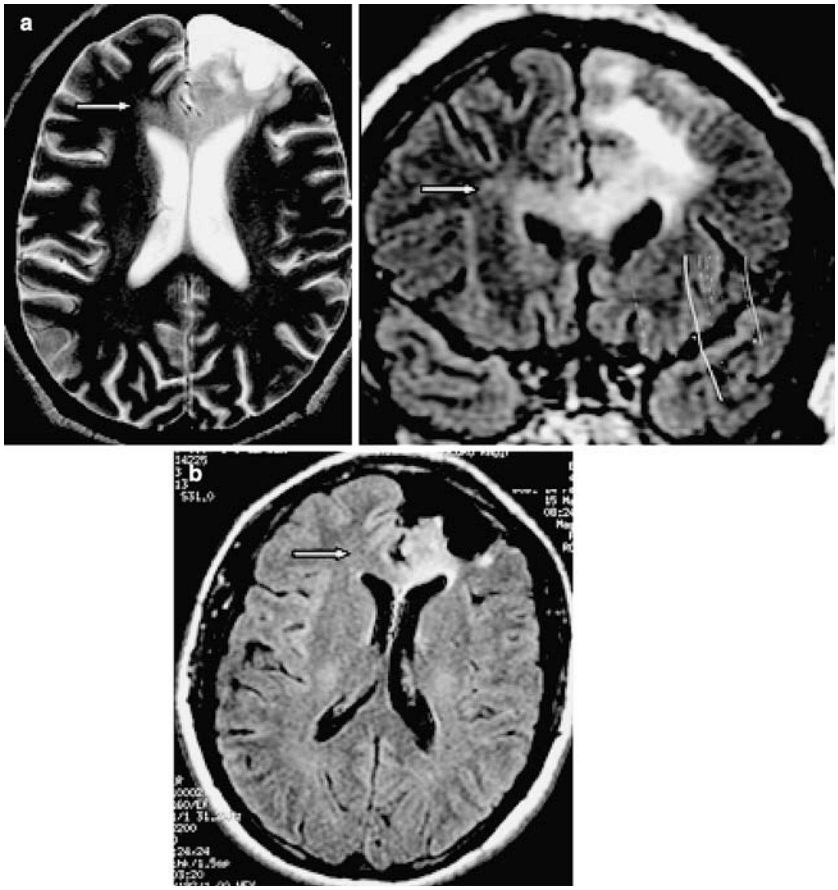

Fig. 2 Axial T2-weighted MRI and coronal FLAIR-weighted MRI, 9 months later, demonstrating a progression of the infiltration of the glioma in the right hemisphere (arrows) (Fig. 2a). Axial FLAIR-weighted MRI after 8 cyles of TMZ, showing a regression of the invasion within the controlateral hemisphere (arrow) (Fig. 2b)

hemisphere and the corpus callosum at the end of the resection was examined, and no tumoral cells were found (Ki 67 nil).

There was no loss of heterozygosity on chromosomes 1p and 19q.

Moreover, the postoperative MRI showed a complete resection, namely with no signal abnormality (Fig. 3)—according to Berger's classification [1].

On the basis of the anatomopathological results and the quality of resection, no other complementary treatment was given. The patient continued to lead a normal life, with a normal neurological examination, and a Karnofsky Performance Score at 100. He had no seizure despite the interruption of the Carbamazepine.

There has been no recurrence on the sequential MRIs performed every 6 months, with a follow-up of 2 years (i.e. 3.5 years since the first symptom).

Discussion

We report the first case of an adult patient operated on for a supratentorial progressive LGG with a complete resection, made possible by a preoperative chemotherapy, which allowed the regression of the peripheral infiltration initially involving unresectable brain areas.

It is surprising that such a strategy was, to our knowledge, never reported in supratentorial grade II glioma in adults. Indeed, administration of neoadjuvant chemotherapy in inoperable tumor, with the aim to induce a regression of the lesion, then to consider an additional surgery, is a management classically reported in non-neurological pathologies. For instance, the use of chemotherapy prior to radical surgery was usually reported for advanced testicular cancer [12], bladder cancer [13], cervical carcinoma of the uterus [14], breast cancer [15] or in lung cancer [16].

Conversely, although scarcely reported in malignant glioma [17, 18], preoperative chemotherapy was never suggested in LGG. This can be explained by the fact that chemotherapy was not considered as a therapeutic option in LGG during many decades. Nevertheless, recent developments have led to an increased interest in chemotherapy for treating LGG. First, it is currently admitted that LGG is not a "benign" tumor, but a preneoplastic lesion that systematically evolves to a malignant glioma [4]. Second, recent series have demonstrated that LGG is chemosensitive, with both

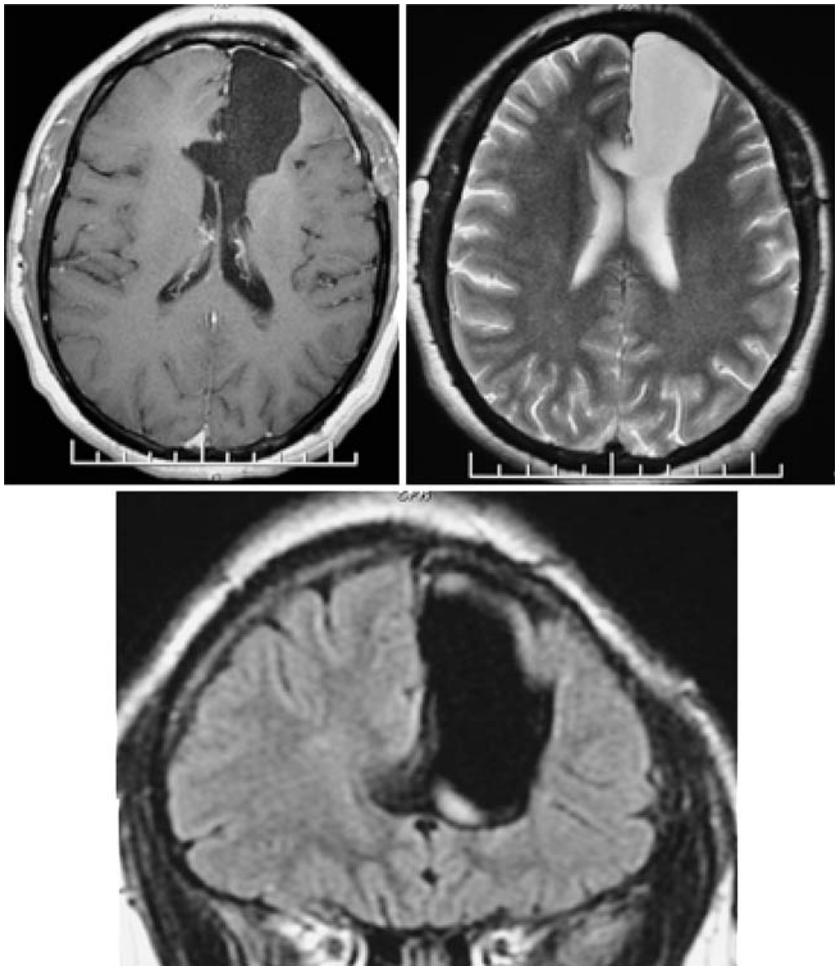

Fig. 3 Axial enhanced T1-weighted and T2-weighted MRI, and coronal FLAIR-weighted MRI, 18 months following the second surgery, showing a complete resection with no recurrence (without any complementary treatment)

clinically relevant responses and disease stabilization or even regression [7–9]. Third, a recent approval of TMZ for treatment of gliomas has provided an impetus for conducting trials in this area [6]. Fourth, advances in molecular biology have enabled to provide some predictive factors regarding both the spontaneous prognosis and response to chemotherapy [7, 19].

As a consequence, it has been recently suggested to use TMZ as initial treatment for adults with supratentorial LGG [7], following a surgery or even when the LGG was unresectable (after a biopsy to confirm the histological diagnosis). TMZ was well tolerated, even with 51% of clinical improvement, particularly in patients with uncontrolled epilepsy [7]. Furthermore, an objective radiologic response was observed, from 31% to 61% of cases [7–9]. More recently, using Procarbazine, Lomustine and Vincristine, Stege et al. have described that 13 out of 16 newly diagnosed LGG showed evidence of response [20].

Surprisingly, to our knowledge, no patient was operated on following chemotherapy. Nonetheless, the follow-up in the chemotherapy studies is very short, between 12 and 24 months, while surgical series using postoperative MRIs have a follow-up between 4 and 5 years [1, 2]. Whereas this delay is still insufficient to definitely conclude about the long-term results, these surgical studies have provided strong arguments in favor of an actual impact of total resection on the natural history of LGG. Thus, in cases of uncompletely resectable LGG, it seems logical to try to combine both treatments.

Our case report is a good illustration of such a therapeutic association. Indeed, following a first surgery with only partial resection, partly due to the fact that intraoperative mapping was not used while the LGG was located near functional areas, the residual tumor continues to growth and to migrate along white matter tracts [21]. Because of an invasion of the right hemisphere (more than two centimeters) through the corpus callosum, the tumor became unresectable—since the preservation of the controlateral homologous is essential in order to recover the function after a surgical resection of a glioma involving fronto-mesial precentral structures, especially the supplementary motor area [10]. Interestingly, 6 cycles of TMZ have allowed the regression of this controlateral infiltration (the tumor shrink stopped during the last cycles). Thus, the tumor became resectable. It is worth noting that the second surgery was performed according to functional boundaries, namely in an awake patient with intraoperative cortico-subcortical sensorimotor and language mapping, in order to preserve the eloquent structures while optimizing the quality of the resection [22]. Using this combination of methods (i.e. neoadjuvant chemotherapy with subsequent radical surgery), the patient continues to have a normal socio-professional life, even with an improvement of his quality of life thanks to a control of epilepsy. In addition, there is no recurrence on control MRIs, with a follow-up of 2 years—while this patient had seizures due to an unresectable progressive LGG involving eloquent areas in July 2003.

The last remarkable point is that the 1p 19q status, while statistically correlated to the prognosis [19] and to the radiological response to chemotherapy [7], does not appear to be a reliable marker for guiding therapeutic decision *at the individual scale*. Indeed, despite no deletion in our case, there was an important shrink of the glioma under TMZ, enabling the adjuvant complete resection.

Conclusions

On the basis of this observation, we propose a new therapeutic strategy in progressive LGG invading critical regions, thereby preventing a complete surgical resection. In these cases, in line with the results previously reported in non-neurological tumors, rather than performing a partial resection, we suggest to perform an initial chemotherapy, with the aim to reduce tumor volume and/or infiltration, and thus to improve surgical resectability. Therefore, additional surgery can be considered, if the LGG becomes operable, according to functional criteria. A second-line chemotherapy and/or radiotherapy can be reserved in case of future recurrence [23].

Of course, further studies with additional cases are necessary in order to validate such a strategy for the treatment of LGG involving eloquent areas. Furthermore, a longer follow-up is mandatory with the goal to actually demonstrate whether a tumor responsive to chemotherapy benefits in duration survival with additional resection. Nevertheless, it seems that such a treatment strategy, very common in the treatment of other solid tumors, might be envisioned in adult neurooncology, particularly in LGG.

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