Diffuse WHO Grade II glioma (diffuse low-grade glioma [DLGG]) is an infiltrative brain tumor that will inevitably grow and become malignant. As recommended by the European Guidelines, extensive resection should be proposed, even beyond the abnormality visible on FLAIR MR images when possible. Indeed, early and radical surgery has been reported to significantly increase the overall survival. Local tumor recurrence is nonetheless usual. In these cases, additional surgery (or surgeries) should be considered because reoperation also has an impact on the course of the DLGG. Such a multistage surgical approach with preservation of the quality of life can be conceived only because mechano-
isms of neuroplasticity exist; this approach may allow an improvement in the subsequent resection or resections, even in eloquent areas.3,7 When surgery is not possible due to massive involvement of functional structures, chemotherapy or radiotherapy can be administered to control the tumor progression, while sometimes reopening the door to resection if DLGG shrinkage has occurred.1

However, although this tumor usually migrates along the white matter fibers,10 before its malignant transformation DLGG can be considered as a regional disease, as supported by the fact that focal treatment such as surgery has a significant impact on the natural history of this tumor, even though there is a tendency for the tumor to recur locally. Multicentric LGGs have been reported in only a few series; again, it was shown that each lesion can be controlled by locoregional resection or resections.21 In this setting, the delayed CSF dissemination of supratentorial DLGGs is an exceptional entity and is rarely described in adults.

Here, we report the oncological results in a surgical series of 9 patients with DLGGs (oligodendroglial, astrocytic, and mixed gliomas) with subsequent leptomeningeal and/or subependymal seeding (LMSS) following multiple incomplete resections. Our aim was to define the clinical, radiological, and pathological features of this rare complication, as well as to discuss its therapeutic management and prognosis.

**Methods**

**Selection of Patients**

We performed a retrospective review of adult patients in our prospective medical record who were surgically treated for supratentorial DLGGs between March 1998 and December 2012. Patients with LMSS were included in this study. Information regarding clinical features, surgical procedures, histopathological results, adjuvant treatment, and clinical outcomes was collected and analyzed.

**Surgical Procedure**

Surgery was proposed with the aim of maximal tumor resection while preserving brain function. To achieve this goal, awake surgery with intraoperative functional brain mapping using cortical and subcortical electrical stimulation was performed in all cases, except during the first operation in Case 2 (surgery was performed at another hospital). Technical details of our functional-guided surgical procedure have been described in previous reports.5,6 The extent of resection was determined on early postoperative FLAIR MR images obtained within 24 hours after surgery. Complete removal of the hyperintense area on postoperative FLAIR MR images was considered as gross-total resection, while residual volume on FLAIR images was defined as incomplete resection (subtotal resection when the residual volume was less than 10 ml and partial resection in all other cases).3

**Postoperative Course**

Postoperatively, patients underwent regular follow-up in the outpatient clinic 3 months after surgery and then every 6 months. The focal regrowth of the tumor and its treatments, that is, additional surgery or surgeries as well as eventual adjuvant chemotherapy and/or radiotherapy were collected. The onset of LMSS, its eventual treatment, and the clinical evolution were also documented. The log-rank test was used to compare 2 Kaplan-Meier survival curves, that is, patients treated using salvage chemotherapy and patients not treated after LMSS diagnosis (p values < 0.05 were considered significant).

**Results**

Clinicopathological features, therapeutic management, and outcome of the 9 patients are summarized in Table 1.

**Patient Population**

Among 400 patients reviewed, 9 patients met the inclusion criteria and were selected. These 9 consecutive patients accounted for 2.25% of the surgically treated patients with DLGGs in our series. There were 6 men and 3 women, whose mean age was 35.5 years (range 22–59 years) at the time of initial symptom onset. Seizure was noted as the initial clinical symptom in all patients except one, in whom the discovery was made due to intracranial hypertension. No patient had a preoperative neurological deficit.

Eight tumors involved the frontal lobe (left hemisphere in 6 cases and right hemisphere in 2 cases), and 1 tumor was located within the left occipital lobe. There was no involvement of the deep gray nuclei, brainstem, or cerebellum in this series. The mean preoperative tumor volume was 68 cm³ (range 32–162 cm³).

**Postoperative Course**

Because of the infiltration of eloquent structures, incomplete tumor removal was achieved in the 9 cases, with 8 subtotal resections and 1 partial resection (this surgery was performed under general anesthesia with no mapping at another institution). There was no permanent neurological worsening. Histopathological examination revealed a WHO Grade II glioma in all patients (7 oligodendrogliomas, 1 astrocytoma, and 1 oligoastrocytoma); 1p19q was codeleted in 5 cases and intact in 4 cases. No immediate postoperative adjuvant treatment was given, and all patients returned to a normal social and professional life.

**Therapeutic Management of Tumor Regrowth**

Because of a rapid regrowth of the residual tumor (in Case 7 after a pregnancy), 5 patients benefited from adjuvant chemotherapy with temozolomide (along with radiotherapy in Case 8 because of the onset of a focal enhancement). After a transient period of stabilization, all the tumors regrew, including the 4 LGGs for which no adjuvant treatment had been given. In addition, focal enhancement occurred in 6 cases. Thus, reoperation was performed in all 9 patients, with a mean interval of 46.5 months (range 14–86 months) between surgeries. The tumor removal was again incomplete in all cases (9 subtotal resections). No patient had a permanent neurological defi-
Leptosubependymal seeding of DLGG

However, neuropathological examination demonstrated a malignant transformation in the 6 patients with imaging enhancement before the second surgery (2 anaplastic oligodendrogliomas, 1 anaplastic oligoastrocytoma, and 3 glioblastomas). Therefore, radiotherapy combined with chemotherapy (temozolomide) was administered to the 5 patients who had not yet undergone radiotherapy (Cases 1, 4, 6, 7, and 9), while chemotherapy alone ( fotemustine) was given to the patient who had already received radiotherapy and temozolomide (Case 8).

In the 3 other patients in whom the diagnosis of DLGG was confirmed, 1 patient (Case 3) did not receive adjuvant treatment, and temozolomide was introduced in the other 2 other patients (Cases 2 and 5) after several months of follow-up because the residual tumor regrew. Finally, these 3 patients benefited from a third surgery after enhancement was observed on imaging. The glioma removal was incomplete in the 3 cases (subtotal resections). There was no permanent neurological deficit. Neuropathological examination revealed malignant transformation in all 3 cases (2 anaplastic oligodendrogliomas and 1 anaplastic astrocytoma). As a consequence, the 3 patients benefited from radiotherapy, followed by chemotherapy (temozolomide) in Case 5 due to a progressive enhancement.

Leptomeningeal and/or Subependymal Seeding

Although the 9 patients were clinically stable after these multiple treatments, they suddenly worsened, with a mean delay of 77 months (range 27–140 months) after initial symptom onset. A control MRI revealed enhancement in the fourth ventricle (Cases 1, 4, 6, 7, and 8) (Fig. 1), subependymal enhancements disseminated along the ventricles (Cases 5 and 9) (Figs. 2 and 3), a diffuse leptomeningeal enhancement around the brain (Case 2), and a diffuse leptomeningeal enhancement around the brain, brainstem, and spinal cord up to the cauda equina (Case 3).

Three patients (Cases 1, 5, and 7) experienced a rapid deterioration in their clinical status. Palliative care was chosen, with no other adjuvant therapy. They died within 2–3 months. The other 6 patients benefited from salvage chemotherapy (bevacizumab), which provides transient stabilization of the disease. Of note, 1 patient (Case 9) developed hydrocephalus due to progression of the intraventricular tumor, and a ventriculoperitoneal shunt was placed. These 6 patients died within 3–38 months (mean 15 months). The median survival in these patients was significantly longer than in the 3 patients who did not undergo salvage chemotherapy ($p = 0.03$).

For the entire population, the mean delay between the diagnosis of LMSS and death was 11 months (range 2–38 months); the mean delay between the initial symptom and death was 88 months (range 34–144 months).

**Discussion**

Although CSF dissemination has occasionally been reported in children with malignant gliomas$^8$ and more rarely in children with low-grade gliomas$^9$ (especially in brainstem gliomas),$^{12}$ LMSS is an exceptional complication in supratentorial DLGGs in adults.$^{13–17}$ Indeed,
Roldán et al.\textsuperscript{16,17} found that LMSS occurred in 3.9% of patients with oligodendrogial tumors and only in 1% of patients with nonmalignant oligodendrogliomas. Here, we report a series of 9 patients with supratentorial oligodendroglial, astrocytic, and mixed low-grade gliomas who developed LMSS, among an overall population of 400 patients with DLGGs managed at our institution between 1998 and 2012. Thus, the prevalence in our experience is 2.25%, in agreement with the previous literature.\textsuperscript{16,17} Even if LMSS can be observed at the time of tumor diagnosis in malignant gliomas,\textsuperscript{8} it was described at the time of disease progression in DLGG,\textsuperscript{13–17} as in our series. We should nonetheless emphasize that, in all patients, leptomeningeal spread occurred in tumors that had progressed to a higher grade of malignancy prior to dissemination. In other words, LMSS occurred in patients with high-grade gliomas that had started as DLGGs.

The mean age of our patients at diagnosis was 36 years, and 6 patients (66.67%) were male, which is in line with classic series of DLGGs without LMSS.\textsuperscript{2} Interestingly, 8 patients (88.9%) had a tumor involving the frontal lobe, in line with other studies showing a predilection of this location for DLGG with CSF dissemination.\textsuperscript{16} Seven of 9 patients had WHO Grade II oligodendroglioma, and 1 patient had a mixed oligoastrocytic glioma. As already reported in the literature, this may suggest that the majority of DLGGs with LMSS have an oligodendrogliomatous component.\textsuperscript{13–17} However, in our series, 1 patient had an astrocytoma, showing that CSF seeding is possible even in supratentorial astrocytic gliomas in adults. Five of 9 patients had a 1p19q deletion; there was no 1p19q loss in the 2 patients with astrocytoma and oligoastrocytoma. Thus, even if the number of patients in this case series is small, it seems that molecular biology is not directly related to the risk of LMSS.

Regarding the treatment given before LMSS, it is worth noting that all patients underwent multiple (2 or 3) incomplete resections. Of note, in our database, 81 (20.7%) of the 391 patients without dissemination underwent multiple operations, whereas 9 (100%) of the 9 patients with dissemination underwent multiple operations (p < 0.0001). Interestingly, because the tumors in all patients contacted the wall of the ventricular system, the ventricle was opened in all 9 cases. Nonetheless, although a large opening of the ventricle was suggested as a possible increased risk for CSF dissemination in high-grade gliomas,\textsuperscript{8} it seems difficult to apply this concept in DLGGs. Indeed, in our experience, 241 patients underwent maxi-
Leptosubependymal seeding of DLGG

Fig. 2. Case 5. A: Axial T2-weighted MR image showing a right frontal DLGG in a 22-year-old man who experienced seizures. B: Axial FLAIR MR image (left) and axial enhanced T1-weighted MR image (center) obtained after 3 surgeries, demonstrating incomplete removal of a tumor now diagnosed as an anaplastic glioma according to the third neuropathological examination. Of note, there was no subependymal seeding at this time, including at the level of the occipital horn of the ventricle (right). C: Axial enhanced T1-weighted MR image showing subependymal seeding along the ventricles, with dissemination around the left occipital horn (arrowhead) as well as in the left lateral horn (arrow), despite radiotherapy and chemotherapy. Due to a poor neurological status, no salvage chemotherapy was given, and the patient died 3 months after the diagnosis of LMSS (83 months after the first symptom).

Excision for DLGGs, with tumor removal extended up to functional boundaries identified with intraoperative electrical mapping, and with opening of the ventricle;\textsuperscript{5,6} no LMSS was observed except in the 9 patients reported here. However, we should acknowledge that, because our 9 patients already had high-grade tumors at the time of their last operation, the ventricular opening could have contributed to the CSF dissemination in this subseries. In addition, it could be suggested that the number of surgeries with incomplete tumor resection may represent a risk factor for CSF dissemination. Indeed, in their population-based study, Roldán et al.\textsuperscript{16} described that the only clinical factor statistically associated with CSF spread was the number of tumor recurrences. Thus, because a lesser extent of resection is significantly associated with a higher risk of early regrowth and higher risk of malignant transformation,\textsuperscript{2,19} the 9 patients had multiple relapses despite repeated surgeries, ultimately with histologically proven anaplastic changes in all cases. In the same way, while it has also been suggested that radiotherapy and chemotherapy could contribute to CSF dissemination in cases of high-grade gliomas due to a depressed immune function,\textsuperscript{8} the percentage of DLGG patients with LMSS is too low (1%) to envision a direct correlation between CSF spread and adjuvant treatments, because these treatments are frequently performed in patients with DLGGs.\textsuperscript{4} In addition, although our patients received temozolomide or fotemustine, none received bevacizumab before spread to the lep-
tomeninges, which has been controversially implicated in remote progression of glial tumors.22

The mean delay between the initial symptom and LMSS was 77 months (range 27–140 months). Although clinical deterioration may be subtle, 3 patients (33%) experienced sudden and dramatic neurological worsening and therefore were unable to undergo salvage treatment. The most frequent pattern of dissemination revealed on MRI was a spread into the fourth ventricle (5 cases). However, other patterns such as subependymal dissemination along the ventricles (2 cases), diffuse leptomeningeal spread around the brain (1 case), and diffuse leptomeningeal spread around the brain, brainstem, and spinal cord up to the cauda equina (1 case) were observed. Subependymal dissemination was treated by chemotherapy (bevacizumab) in 6 cases with preservation of a normal general and neurological status at diagnosis of LMSS. These 6 patients died within 3–38 months (mean 15 months), which is a significantly longer survival than that for the 3 patients who did not receive salvage chemotherapy and died within 2 to 3 months.

In the entire series, the mean delay between initial symptom onset and death was 88 months (range 34–144 months), which is short in comparison with an overall survival of about 15 years that was recently reported in a large surgical series with more than 1097 patients with DLGG.22

We should nonetheless acknowledge that among 400 patients reviewed, we selected only adult patients who were surgically treated for supratentorial DLGGs. As a consequence, it is possible that other patients with DLGG developed CSF dissemination but were not included in our study because they did not undergo surgery for their glioma. This possible bias could induce an underestimation of the rate of delayed LMSS in DLGGs.

Conclusions

Cerebrospinal fluid dissemination of a DLGG is a rare but possible event. It can occur throughout the progression of WHO Grade II oligodendrogliomas, oligoastrocytomas, and astrocytomas, regardless of the 1p19q status. This complication seems to appear in patients who undergo multiple incomplete resections. Salvage therapy could be considered in patients with good neurological status. However, LMSS is associated with a decreased overall survival. Therefore, this rare entity deserves further multicenter studies to better understand its pathophysiology and to adapt therapeutic and possibly even preventive strategies.

Disclosure

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

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References


6. Gil-Robles S, Duffau H: Surgical management of World Health
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Organization Grade II gliomas in eloquent areas: the necessity of preserving a margin around functional structures. Neurosurg Focus 28(2):E8, 2010

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