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The landscape of postsurgical recurrence patterns in diffuse low-grade gliomas

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ABSTRACT

Early and maximal safe surgical resection optionally followed by adjuvant treatment is currently recommended in diffuse low-grade glioma (DLGG). Although this management delays malignant transformation (MT), recurrence will most often occur. Because this relapse usually arises locally, reoperation can be considered, with possible further chemotherapy/radiotherapy. However, due to a prolonged overall survival, a large spectrum of unusual recurrence patterns begins to emerge during long-term follow-up, beyond the classical slow and local tumor re-growth. We review various atypical patterns of DLGG relapse, we discuss their pathophysiological mechanisms and how to adapt the treatment(s). Those patterns include very diffuse, ipsi- or bilateral gliomatosis-like progression, multicentric recurrence with emergence of remote low-grade or high-grade glioma, leptomeningeal dissemination, acute (early or delayed) local MT or bulky relapse into the operating cavity. This landscape of recurrence patterns may allow physicians to elaborate new tailored therapeutic strategies and scientists to develop original hypotheses for basic research.

1. Introduction

Diffuse low-grade glioma (DLGG), i.e. grade II glioma according to the World Health Organization (WHO) classification, is a rare disease accounting for about 7% of primary brain tumors (Ostrom et al., 2017). If left untreated, this tumor will constantly grow, it will migrate along the brain pathways and finally it will progress to a higher grade of malignancy, leading to functional impairment and life-threatening situation (Duffau, 2017). An improved understanding of the natural course of DLGG has resulted in a paradigmatic shift in patient management, from a traditional watchful policy to early treatment strategies (Duffau and Taillandier, 2015). Indeed, thanks to an active therapeutic attitude, in particular starting with maximal surgical resection, the overall survival (OS) has approximately doubled, by postponing malignant transformation (MT) (Duffau, 2018a, 2018b). In old series in which there was no attempt to perform precocious radical removal, the OS was about 6–7 years (Pignatti et al., 2002; van den Bent et al., 2005), whereas in recent experiences based upon early surgery, the OS is around 14–15 years (Capelle et al., 2013; Jakola et al., 2017; Roelz et al., 2016; Smits et al., 2008). In addition, surgical advances such as intraoperative functional mapping, especially in awake patients, enabled a significant decrease of surgical complication rates, even in areas deemed to be critical, with nonetheless an improvement of the extent of resection (De Witt Hamer et al., 2012; Ferracci and Duffau, 2018). Whereas a simple surveillance can be considered after (sub)total DLGG excision, adjuvant oncological therapies may be discussed when only partial resection has been achieved for functional reasons (e.g., tumoral involvement of the white matter connectivity which cannot be compensated if surgically damaged) (Soffietti et al., 2010).

However, despite the oncological benefit of this personalized therapeutic approach, a relapse will most often occur, due to the invasive nature of this neoplasm. Such tumors have been defined as low versus high risk of recurrence according to several markers. For example, the UCSF team developed a score based upon 4 markers, that is, location in presumed eloquent cortex, age more than 50 years old, KPS score 80 or less and maximal diameter more than 4 cm, that was shown to predict

Abbreviations: CSF, cerebrospinal fluid; DLGG, diffuse low-grade glioma; FLAIR, fluid-attenuated inversion recovery; GC, gliomatosis cerebri; GFAP, glial fibrillary acidic protein; IDH, isocetrate dehydrogenase; LMD, leptomeningeal dissemination; MT, malignant transformation; OS, overall survival; WHO, World Health Organization; VEGF, vascular endothelial growth factor

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progression free survival and OS (Chang et al., 2009). In the same way, Chaichana et al. reported factors associated with recurrence, i.e., tumor size, enhancement, duration of longest lasting symptoms, as well as factors associated with MT, such as tumor size, pathology and gross total resection (Chaichana et al., 2010).

However, the patterns of relapse have not been specifically investigated. In the vast majority of patients, DLGG will recur slowly and locally, opening the door to a possible reoperation, optionally followed by chemotherapy or radiotherapy (Duffau and Taillandier, 2015). Again, the goal is to delay MT by controlling the residual tumoral disease around the surgical cavity. Interestingly, because of a prolonged OS in DLGG (nowadays over 10 years), this typical scenario of slow and local tumor re-growth around the surgical cavity is often replaced by a large spectrum of unusual recurrence patterns that starts to be observed during long-term follow-up. Understanding these patterns is crucial to tailor an individualized therapeutic strategy with the aim of optimizing the onco-functional balance, namely, to prolong OS while increasing the time with a normal quality of life (Mandonnet and Duffau, 2018). We aim here to review these different clinical and radiological scenarios of relapse and to discuss their potential pathophysiological mechanisms in order to elaborate new tailored management.

2. Classical postsurgical pattern of slow and local DLGG re-growth

For most DLGG patients, the glioma recurrence arises locally, within a few millimeters to centimeters around the surgical cavity (or within the field of radiation if the patient has been irradiated following surgery) (Fig. 1). This can be explained by the fact that conventional MRI underestimates the actual spatial extent of DLGG, as demonstrated by biopsy samples that identified tumoral cells up to 2 cm beyond the area of signal abnormalities, even for gliomas well defined on MRI (Pallud et al., 2010; Zetterling et al., 2016). Therefore, except in some cases of supratotal resection (i.e. with the removal of a security margin around the FLAIR-signal abnormalities) when the tumor is located in non-eloquent brain structures (Yordanova et al., 2011), these glioma cells are usually left around the surgical cavity in order to preserve the quality of life. Indeed, since the resection is stopped when neural networks crucial for brain functions are detected by intrasurgical electrostimulation mapping, both at cortical and subcortical level, if tumoral cells already infiltrate these eloquent pathways, in essence it is not possible to remove them (Duffau, 2018a, 2018b). This is very frequent because DLGG has a propensity to migrate along the subcortical white matter fibers

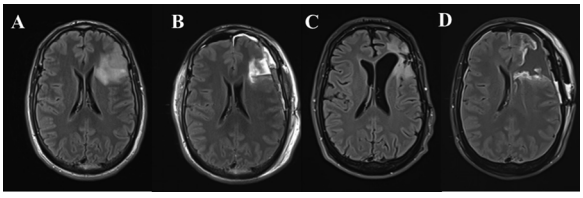

Fig. 1. (A) Preoperative axial FLAIR-weighted MRI in a 36-year-old right-handed man who experienced seizures, with a left frontal DLGG. The neurological examination was normal. (B) Immediate postoperative axial FLAIR-weighted MRI, showing a subtotal resection performed under awake mapping. A WHO grade II oligodendroglioma (IDH1 mutated, 1p19q codeleted) was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 6 months. (C) Axial FLAIR-weighted MRI achieved 5 years following surgery revealing a typical pattern of glioma progression, with a slow tumoral regrowth around the surgical cavity, with no enhancement (not shown here) in an asymptomatic patient. Reoperation was proposed to decrease again the tumoral volume. (D) Immediate postoperative axial FLAIR-weighted MRI, showing a total resection performed under awake mapping. A WHO grade II oligodendroglioma was confirmed. No adjuvant treatment was administrated. The patient resumed a normal life, with a regular surveillance (follow-up of 4 years since reoperation).

(Mandonnet et al., 2006) and these bundles represent a major limitation of neuroplasticity (Duffau, 2015). Moreover, even though DLGG is generally re-growing slowly, with the same velocity diameter expansion than before surgery, tumor cells will continue to proliferate and eventually acquire new mutations leading to their MT (Scribner et al., 2017).

Thus, regarding clinical implications, in this typical pattern of pericavitary DLGG recurrence, repeat surgery is the first treatment to be discussed (Fig. 1). Indeed, maximal cytoreduction can favorably impact OS by reducing the statistical probability of a second-hit mutation (Sanai and Berger, 2018). From a functional point of view, optimization of the extent of resection can be achieved while preserving brain functions thanks to mechanisms of neural reorganization promoted by the tumor growth and previous surgery itself (Capelle et al., 2013; Martino et al., 2009). Regarding epilepsy, Picart et al. showed that the incidence of seizures was significantly lower at reoperation than before the first removal, with constant decrease of drug resistance in concerned patients (Picart et al., 2018). Furthermore, in a series of patients who underwent repeat surgeries for DLGG re-growth, Martino et al. reported that, in 9 of 17 patients with chronic epilepsy before reoperation, the seizures disappeared, and in 5 patients, there was a reduction in the frequency and intensity of the seizures (Martino et al., 2009). Of note, because the potential of neuroplasticity is lower when glioma relapse involves mainly subcortical bundles rather than cortical areas (Picart et al., 2018), neoadjuvant chemotherapy has been proposed in order to induce tumor shrinkage and then to reopen the window to subsequent surgical excision (Blonski et al., 2013). Importantly, irradiation of these white matter bundles may result in delayed cognitive disturbances (Douw et al., 2009). This has led some authors to defer radiation therapy in DLGG (Bady et al., 2018), including in case of slow and local relapse (Duffau and Taillandier, 2015).

3. Atypical postsurgical pattern of DLGG relapse

3.1. Very diffuse progression “gliomatosis-like”

As mentioned, glioma cells often migrate along white matter tracts (Mandonnet et al., 2006). Although the tumoral cells can mainly follow the short-U fibers, leading to an invasion that remains local or regional (in line with the typical pattern of re-growth previously described), they can also follow the associative, projection and commissural fibers, then invading the brain diffusely over long distances, without necessarily requiring angiogenesis (Lamszus et al., 2003). Invasion of the corpus callosum with bi-hemispheric extension is a typical example of such a diffuse progression (Duffau et al., 2004). From a radiological point of view, a DLGG which was originally focal and that secondarily progresses in a highly invasive fashion (Fig. 2) has been called a secondary gliomatosis cerebri (GC) (Herrlinger et al., 2016). The 2007 WHO classification described GC as an extensively infiltrative glioma involving at least three contiguous cerebral lobes (Louis et al., 2007). However, from a neuropathological perspective, since there is no significant difference between DLGG and GC, this entity was removed from the 2016 WHO classification (Louis et al., 2016).

Even though the mechanisms of this shift from a proliferative to a migratory glioma is still unknown, a possible modification of molecular profile could be hypothesized. Indeed, in the era of radiomics, correlations between the IDH-1p19q status and the delimitation of DLGG borders on MRI (sharp or indistinct) have been reported (Darlix et al., 2017). Although the frequency of IDH1 mutation was lower in primary GC (41%) compared to DLGG (70%) (Kwon et al., 2012), this remains to be demonstrated in secondary GC. Gliomas seem to use the same tortuous extracellular routes of migration that are travelled by immature neurons and stem cells, frequently using blood vessels as guides (Giese and Westphal, 1996). They repurpose ion channels to dynamically adjust their cell volume in order to accommodate to narrow spaces and breach the blood–brain barrier through disruption of astrocytic end

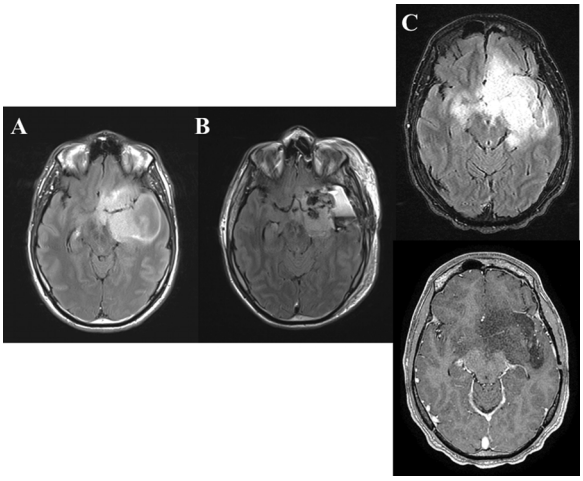

Fig. 2. (A) Preoperative axial FLAIR-weighted MRI in a 26-year-old right-handed man who experienced seizures, with a left paralimbic DLGG. The neurological examination was normal. (B) Immediate postoperative axial FLAIR-weighted MRI, showing a subtotal resection (residue of 7cc) performed under awake mapping. A WHO grade II glioma (IDH1 mutated, 1p non deleted, 19q deleted) was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 6 months. Due to constant progression of the FLAIR hypersignal on repeated MRI, adjuvant treatment was proposed to the patient, who refused. (C) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 3 years following surgery, revealing a very diffuse pattern of regrowth « gliomatosis-like » with bilateral extension. At that time, the patient accepted to be treated by chemotherapy.

feet, which envelop blood vessels (Watkins et al., 2014). Whereas secondary GC has been profusely described in high grade gliomas treated with anti-VEGF molecule, this pattern can also be found in DLGG, with or without previous antiangiogenic treatment. Indeed, the degree of invasiveness is not necessarily correlated with the grade of malignancy (Fig. 2) (Guthrie and Laws, 1990).

Further studies looking into genetic differences between the first and second surgery are needed, knowing nonetheless that repeat operation is not the most appropriate strategy in this scenario. This is due to the fact that the neuroplastic potential is very limited at the subcortical connectivity level, whereas it is very high at the cortical level (Herbet et al., 2016). Therefore, although it has been proposed to consider more systematically iterative surgeries in order to further decrease the tumoral volume while preserving neural functions, this attitude is possible when the DLGG re-grow at the expense of the cortex (thanks to cortical remapping) but not when the glioma migrated along the main white matter pathways (Picart et al., 2018). Thus, in this GC-like pattern of relapse, a biopsy could be discussed to obtain a new histomolecular tumor profile before administrating adjuvant treatment, even in the absence of any enhancement. In this setting, chemotherapy can be considered as the first therapeutic option, due to the large volume of irradiation necessary for GC-like gliomas and the high risk of induced cognitive deterioration (Douw et al., 2009).

3.2. Multifocal and multicentric progression

Multiple gliomas are very rare, accounting for 2–9% of gliomas (Barnard and Geddes, 1992; Batzdorf and Malamud, 1963; Djalilian et al., 1999; Kyritsis et al., 1992). Multiple gliomas have been classified as two different entities by Batzdorf and Malamud: (i) multifocal gliomas resulting from dissemination via established pathways, therefore implying intertumoral connection; (ii) multicentric gliomas in

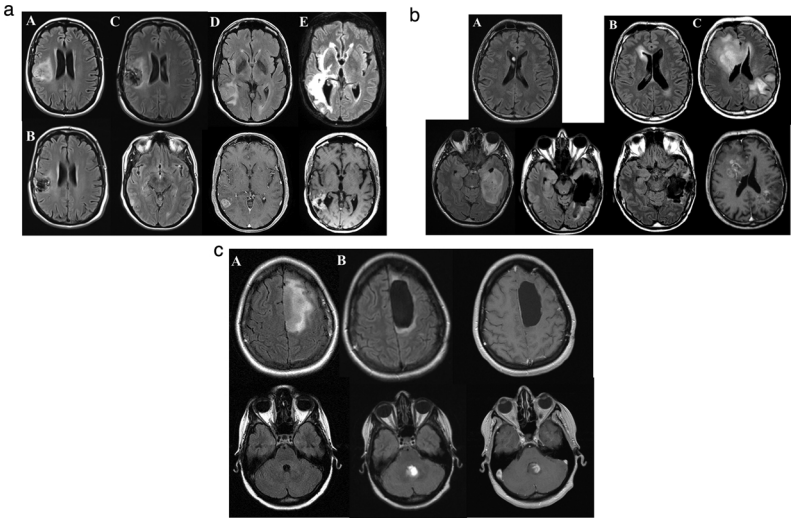

Fig. 3. a (A) Preoperative axial FLAIR-weighted MRI in a 52-year-old right-handed woman who experienced seizures, with a right central DLGG. There was no other signal abnormality (not shown here). The neurological examination was normal. (B) Immediate postoperative axial FLAIR-weighted MRI, showing a subtotal resection performed under awake mapping. A WHO grade II glioma IDH wild-type was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 6 months. (C) Axial FLAIR-weighted MRI achieved 2.5 years following surgery, revealing not only a slow tumoral regrowth around the surgical cavity, but also the occurrence of a second lesion located at the right occipito-temporal junction (with no signal abnormality between both lesions). At that time, PCV was administrated. (D) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 3 months after 6 cycles of PCV, revealing a progression of the second tumor with the occurrence of an enhancement. Surgery was decided on this second tumor. A glioblastoma was diagnosed and a Stupp protocol was administrated. (E) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI at the end of Stupp protocol, revealing a progression of the glioblastoma. Despite Bevacizumab, the patient died 6 months later. b (A) Lower left: preoperative axial FLAIR-weighted MRI in a 58-year-old right-handed man who experienced seizures, with a left DLGG. There was no other signal abnormality, especially at the level of the right frontal lobe (upper). The neurological examination revealed some mild memory disorders. Lower right: Immediate postoperative axial FLAIR-weighted MRI, showing a subtotal resection performed under awake mapping. A WHO grade II glioma 1p-19q codeleted was diagnosed, with nonetheless a focus of malignant transformation. Due to incomplete resection, radiotherapy and chemotherapy were administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 3 months. (B) Axial FLAIR-weighted MRI 5 years following surgery, revealing not only a slow tumoral regrowth at the upper part of the surgical cavity, but also the occurrence of a second lesion in the right frontal lobe (with no signal abnormality between both lesions). At that time, Temozolomide was administrated for one year, with a transitory stabilization then a regrowth of both tumors, leading to give PCV. (C) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 3 months after 3 cycles of PCV, revealing a progression of both tumors with the occurrence of enhancements. Despite Bevacizumab, the patient died 9 months later. c (A) Preoperative axial FLAIR-weighted MRI in a 32-year-old right-handed woman who experienced seizures, with a left fronto-mesial DLGG. There was no other signal abnormality, especially within the posterior fossa. The neurological examination was normal. A complete resection of a DLGG was performed under awake mapping. A WHO grade II oligodendroglioma 1p19q codeleted was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 6 months. (B) Postoperative axial FLAIR (left) and T1 enhanced (right) weighted MRI 2 years later, revealing not only a slow tumoral regrowth around the surgical cavity, but also the occurrence of a second lesion in the vermis. RT-PCV was administrated but the disease progressed. Despite Bevacizumab, the patient died 6 months later.

which the tumors are in different lobe or hemisphere and are completely separated, with no anatomical continuity between them (Batzdorf and Malamud, 1963). They can be synchronous (primary) or metachronous if they develop at different times during the course of the disease (Vergani et al., 2009). Thought to be due to aggressive biological behavior, they were mainly described in high-grade gliomas: nonetheless, this pattern has also been reported in DLGG (Terakawa et al., 2013; Vergani et al., 2009). Indeed, in postoperative DLGG recurrence, the emergence of remote glioma can be observed, in the same hemisphere than the initial DLGG (Fig. 3a), in the contralateral hemisphere (Fig. 3b) or even in the posterior fossa (Fig. 3c) - independently of the possible local re-growth of the initial tumor (or not). This second tumor may be a low-grade or a high-grade glioma, as confirmed by neuropathological examination (Fig. 3a).

Regarding the mechanisms mediating multiple gliomas, Russell and Rubinstein suggested the following classification: (i) spread via commissural or other pathways; (ii) spread via cerebrospinal fluid (CSF) channels; (iii) local metastasis; and (iv) multicentric glioma, which can only be diagnosed by clinicopathological examination (McLendon et al., 2006). The Conheim's theory suggested multiple embryonal residues scattered in different sites (Bussone et al., 1979). Willis proposed that multicentric lesions result from a twofold process. The first stage (initiation) would be neoplastic transformation over a wide area of the encephalon, the second stage (promotion) would be a process of progressive neoplastic proliferation in different sites (Willis, 1952). Moertel (2012) hypothesized that general carcinogenesis of multicentric neoplasms occurs because of specific intrinsic or extrinsic carcinogenic influences acting on susceptible tissue for a sufficient amount of time to initiate irreversible anaplastic change in the reproductive pattern of the constituent cells. Intrinsic factors could be underlying diseases such as neurofibromatosis, tuberous sclerosis or multiple sclerosis, which promote multicentric neoplastic changes; extrinsic factors could be ionizing radiation exposition. It was also suggested that these gliomas may not be truly multifocal but rather may reflect manifestations of more rapidly proliferating foci within a larger area of microscopically invaded brain (Giese et al., 2003). Of note, the genetic profile could differ between tumors (Vergani et al., 2009).

In practice, it has been demonstrated that multifocal and multicentric DLGGs can be resected safely without generating severe persistent functional deterioration, supporting surgery as the first treatment, as in solitary DLGG (Terakawa et al., 2013; Vergani et al., 2009). Adjuvant therapies may also be discussed in case of metachronous high-grade glioma emerging away from the initially removed DLGG.

3.3. Leptomeningeal dissemination

Leptomeningeal dissemination (LMD) is defined as tumor cells identified in the CSF or radiological appearance of cranial nerve, extra-axial space or spinal cord involvement. While CSF dissemination has occasionally been observed in the pediatric population with malignant gliomas (Grabb et al., 1992) and more exceptionally with low-grade gliomas (Rondinelli et al., 2008), LMD is a very rare complication in DLGG in adults (Nicolasjilwan et al., 2012; Roldán et al., 2011). Roldán et al. (2011) reported that LMD arose in 3.9% of DLGG with oligodendroglial component and only in 1% of nonmalignant oligodendrogliomas. The prevalence in a series with 400 DLGGs was about 2.25% (Alvarez de Eulate-Beramendi et al., 2014). Delayed CSF spread at DLGG relapse may occur at the level of the leptomeningeal space around the brain, the spinal cord as well as within the ventricles (subependymal seeding) (Fig. 4).

Regarding factors associated with LMD, contact of the initial tumor with CSF is not a prerequisite for such dissemination (Maslehaty et al., 2011). LMD has mainly been observed in recurrent oligodendrogliomas with 1p19q co-deletion (58% of cases) and multiple relapses. However, there is currently no molecular profile that enables the prediction of the onset of LMD, which can arise both in oligodendroglioma (Roldán et al., 2011) and astrocytoma (Alvarez de Eulate-Beramendi et al., 2014). In addition, a recent series reported a frontal lobe location and MT prior to the dissemination in all cases (Roldán et al., 2011). Indeed, CSF seeding usually occurred in neoplasms that had already progressed to a higher grade of malignancy before dissemination, i.e. in high-grade gliomas that had started as DLGG (Fig. 4) (Alvarez de Eulate-Beramendi et al., 2014). This is in agreement with studies which revealed that malignant phenotypes preferentially used other routes of invasion, as spreading along the CSF, rather than white matter migration (Wang et al., 2013). The patients also often underwent multiple operations that lead to opening of the lateral ventricle. Although it has been suggested that surgery may represent one of the major routes of LMD, its prevalence remains nonetheless very low even when extensive resection is achieved (Alvarez de Eulate-Beramendi et al., 2014). Moreover, immunohistochemical study evidenced that leptomeningeal lesions reveal less GFAP expression than the primary tumor (Maslehaty et al., 2011). In glioblastoma patients with GFAP-negative tumors who experienced LMD, there was a marked CSF dissemination but little infiltrative behavior at the primary tumor site - and vice versa for patients with positive GFAP expression. Whether DLGG can demonstrate such a high degree of dedifferentiation has to be proven (Onda et al., 1989). Finally, adjuvant therapy such as chemotherapy and radiation therapy have been proposed as contributing factors due to depression of the immune system, maybe facilitating LMD in children (Grabb et al., 1992).

In practice, LMD at DLGG relapse seems to occur in patients who underwent several incomplete resections. Salvage therapy (e.g. Bevacizumab) could be envisioned in patients with good neurological status. LMD is associated with a decreased OS (Alvarez de Eulate-Beramendi et al., 2014). Therefore, because the prognosis is very poor once LMD occurs, the main goal in DLGG is to avoid MT, thus preventing CSF dissemination until proven otherwise.

3.4. Sudden early or delayed local malignant transformation

The risk of MT in DLGG is highly dependent on the tumoral volume and the growth rate (Pallud et al., 2013). Therefore, after a (sub)total resection with a residual volume less than 10-15cc in a DLGG with a slow velocity diameter expansion, and no histomolecular characteristics of malignant glioma, especially in young patients, the re-growth is most of the time slow (Duffau, 2017). However, in exceptional cases, despite the absence of unfavorable prognostic factors, one could observe a dramatic pattern of recurrence. In this scenario, the tumor which initially followed the typical slow velocity of DLGG, or even was stable in case of (supra)complete resection, undergoes a sudden MT, with an acceleration of the growth rate and a neuroimaging supporting degeneration, especially with the onset of enhancement. Clinically, this acute transformation to a higher grade of malignancy may lead to a neurologic impairment and a life-threatening situation (Rech et al., 2014). Surprisingly, such an atypical pattern of relapse can arise within a few months (Fig. 5a) as well as many years after surgical resection of a DLGG (Fig. 5b). Therefore, those recurrences are very difficult to deal with because of their unexpected nature and because of the current lack of clinical, radiological and neuropathological factors allowing prediction of this sudden MT.

To this end, further extensive molecular analyses should be considered in this subgroup of DLGG, with the aim of identifying genetic markers of early or delayed acute behavioral change of the neoplasm. Indeed, IDH status alone is not reliable enough at the individual level, since the absence of IDH mutation is associated with a heterogeneous outcome (Di Carlo et al., 2018; Poulen et al., 2018). Interestingly, a small fraction of diffuse WHO grade II astrocytomas shows a DMBT1 homozygous deletion which is significantly associated with shorter overall survival (Motomura et al., 2012). MET gain, also common in diffuse astrocytomas, is also associated with shorter survival (Pierscianek et al., 2013). Remarkably, beyond the acute degeneration itself, metaplastic transformation may also be observed, such as

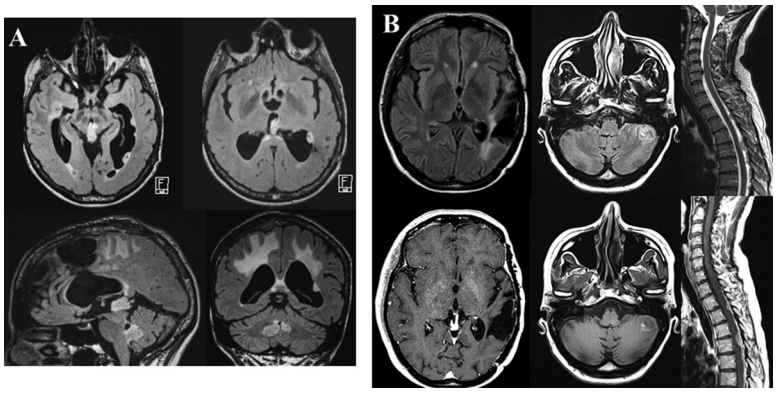

Fig. 4. (A) Postoperative axial FLAIR-weighted MRI 4 years after two consecutive resections of a right frontal glioma in a 44-year-old woman who experienced seizures. While the tumor was a WHO grade II glioma according to the first neuropathological examination, the tumor was diagnosed as a WHO grade III glioma according to the second neuropathological examination. The MRI revealed subependymal seeding along the ventricles, with dissemination around both occipital horns as well as in the sylvian aqueduct and the fourth ventricle, despite radiotherapy and Temozolomide performed following the reoperation. At that time, salvage chemotherapy by Bevacizumab was given, but the patient died 38 months after the diagnosis of LMD. (B) Left: Postoperative axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 3 months after subtotal resection for a left temporal WHO grade II glioma in a 29-year-old woman who experienced seizures. The patient resumed a normal life, with no neurological deficit. Regular MRI was achieved every 6 months, revealing not only a slow tumoral regrowth around the surgical cavity but also the occurrence of an enhancement 4 years later. Again, a subtotal resection was performed under awake mapping. At that time, the neuropathological examination diagnosed a glioblastoma, and a Stupp protocol was administrated, allowing a stabilization of the clinical and radiological status. Middle: Postoperative axial FLAIR (upper) and T1 enhanced (lower) weighted MRI achieved seven years after the first surgery, revealing the occurrence of an enhanced tumor at the level of the left cerebellar hemisphere – while the temporal tumor was stable (not showed here). Moreover, MRI showed LMD along the spinal cord (right). Resection of the cerebellar tumor was achieved, revealing a WHO grade III astrocytoma (IDH1 mutated). Bevacizumab and Lomustine were given, with a transitory clinical improvement for 4 months, with decreasing of leptomeningeal locations. This chemotherapy was stopped due to poor tolerance and the patient died 6 months later.

transformation of WHO grade II glioma with 1p19q codeletion into gliosarcoma several years following surgical resection (Rech et al., 2014). These examples support that further molecular stratification is needed to better understand DLGG relapse.

In practice, the possible occurrence of an enhancement 10 years after complete tumor removal, with no re-growth in the meantime - even in asymptomatic patient (Fig. 5b) - supports the need to achieve a systematic post-operative follow-up based on MRI every 3–6 months throughout life, because the risk of acute and aggressive recurrence can never be ruled out.

3.5. Bulky relapse into the surgical cavity

Although DLGG is by definition an infiltrating neoplasm which invades the brain parenchyma, in exceptional cases, relapse may occur as a tumor mass growing directly into the operative cavity (Figs. 6a and b). These patients are asymptomatic, because the brain itself is not affected by this kind of recurrence, at least at the beginning. Mechanism of this bulky recurrence into the cavity is unclear, but one could hypothesize that it is related to re-progression of tumoral cell for their own account from the vessel wall of from the meningeal tissue. Indeed, two patterns can be identified on MRI: (i) a tumor mass developed along blood vessels running in the surgical cavity (i.e., “in passing”

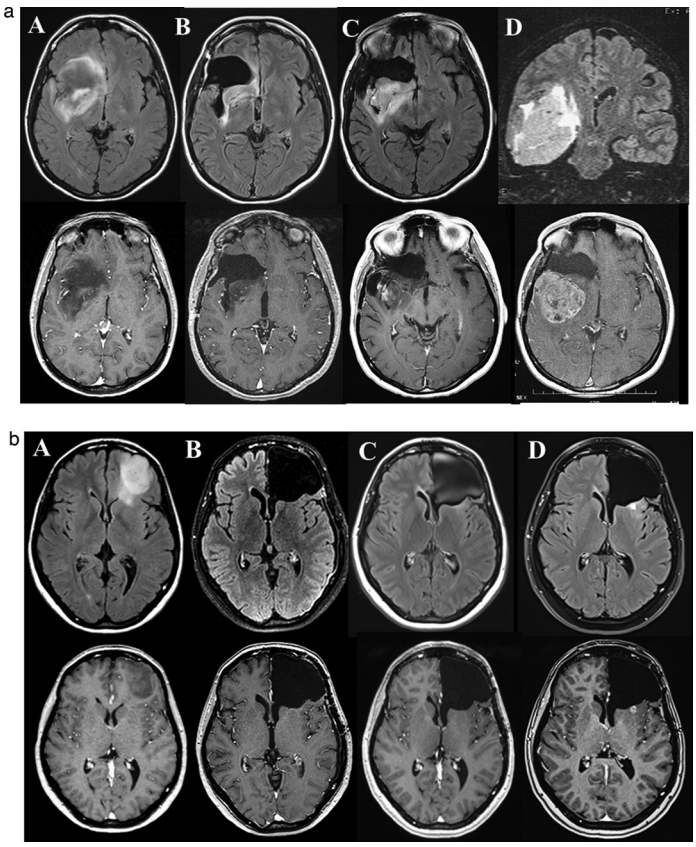

Fig. 5. a (A) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI in a 37-year-old right-handed woman who experienced seizures, with a right paralimbic DLGG. The neurological examination was normal. (B) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI performed 9 months following a subtotal resection (residue of 8cc) performed under awake mapping. A WHO grade II astrocytoma (IDH1 mutated, 1p19q non codeleted) was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. (C) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI achieved 1 year after surgery, in a patient who experienced seizures, showing a sudden increase of the tumoral volume with the occurrence of an enhancement. (D) Coronal FLAIR (upper) and T1 enhanced (lower) weighted MRI after radiotherapy and temozolomide, revealing a rapid progression of the enhancement. The patient died 6 months later despite Bevacizumab and Fotemustine. b (A) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI in a 28-year-old right-handed woman who experienced seizures with a right frontal DLGG. The neurological examination was normal. (B) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 3 months following a supratotal resection performed under awake mapping. A WHO grade II oligodendroglioma (IDH1 mutated, 1p19q codeleted) was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 6 months. (C) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI performed 10 year after surgery, showing a stable imaging, with no FLAIR signal abnormality. (D) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 6 months after the previous MRI, revealing the sudden occurrence of a nodular enhancement in a patient still asymptomatic. At that time, reoperation was performed, with a complete resection. A WHO grade III glioma was diagnosed and chemotherapy was administrated in a patient who resumed a normal life, with no relapse with 1 year of follow-up.

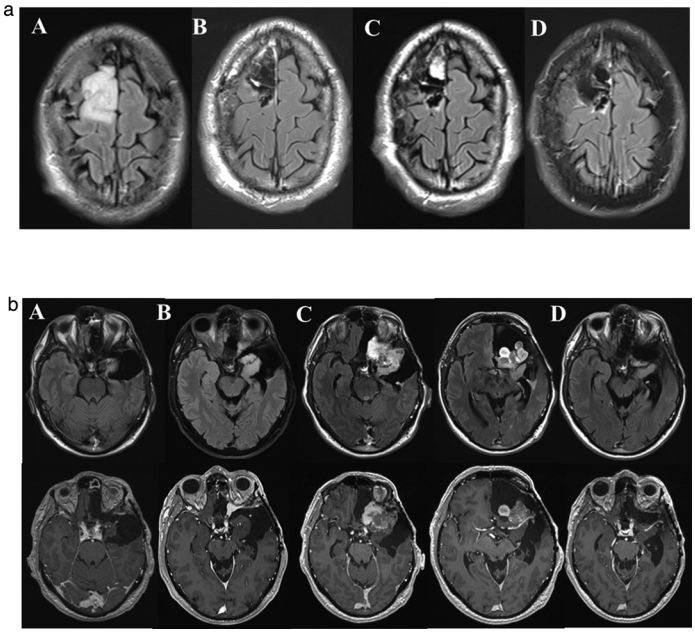

Fig. 6. a (A) Preoperative axial FLAIR-weighted MRI in a 36-year-old right-handed man who experienced seizures, with a left fronto-mesial DLGG. The neurological examination was normal. (B) Immediate postoperative axial FLAIR-weighted MRI, showing a total resection performed under awake mapping. A WHO grade II oligodendroglioma (IDH1 mutated, 1p19q codeleted) was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 6 months. (C) Axial FLAIR-weighted MRI achieved 4 years following surgery, revealing a bulky relapse into the operating cavity, with a tumor mass developed at the expense of the pia matter/arachnoid bordering the cavity in an asymptomatic patient. Reoperation was decided. (D) Immediate postoperative axial FLAIR-weighted MRI after second surgery, showing a total resection. The diagnosis of WHO grade II oligodendroglioma was confirmed. No adjuvant treatment was administrated. The patient resumed a normal life, with a regular surveillance. b (A) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 3 months following a subtotal resection in a 50-year-old right-handed patient who experienced seizures, revealing a small residue around the Sylvian arteries. A WHO grade II oligodendroglioma (IDH1 mutated, 1p19q codeleted) was diagnosed. No adjuvant treatment was administrated. The patient resumed a normal life, with no neurological deficit and no epilepsy. Regular MRI was achieved every 6 months. (B) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 3 years after surgery, revealing a slow re-growth of the residual tumor and the occurrence of an enhancement into the surgical cavity. Because it was an intracavitary relapse in an asymptomatic patient, a simple surveillance was continued. However, two years later, due to a slow but constant tumoral progression, Temozolomide was administrated due to the oligodendroglial nature of the tumor. The patient enjoyed a normal life. (C) Axial FLAIR (upper) and T1 enhanced (lower) weighted MRI 7 years after surgery, showing that the enhanced tumor continued to grow slowly but regularly, with a bulky relapse into the operating cavity in an asymptomatic patient. Reoperation was decided. (D) Immediate postoperative axial FLAIR (upper) and T1 enhanced (lower) weighted MRI after second surgery, showing a subtotal resection, with a small residue around the Sylvian arteries. A WHO grade III oligodendroglioma was diagnosed, and a radiotherapy-chemotherapy was administrated. The patient resumed a normal life, with no neurological symptoms.

vessels preserved during the first resection to avoid stroke); (ii) a tumor mass developed at the expense of the pia matter/arachnoid bordering the surgical cavity. This is due to the fact that tumoral cells may be voluntarily left at this level, since subpial dissection is highly recommended in glioma surgery in order to avoid vascular damages and then to preserve the quality of life (Duffau, 2012). Therefore, it is puzzling to note that intracavitary recurrence is very rare. Of note, this pattern of relapse may be associated or not with a tumoral diffusion within the peri-cavitary parenchyma.

In practice, the treatment is a reoperation, since the neurological risk of surgery in a previous surgical cavity is virtually nil. Surgery usually results in complete removal with no need of adjuvant therapy (Fig. 6a). Of note, such a resection is not emergent, due to the lack of functional symptoms, and should be adapted to the existence of a simultaneous progression in the brain itself - or not.

4. Conclusion

Recurrence in DLGG is almost ineluctable. Even when supramaximal resection has been achieved, with the excision of a safety margin around the FLAIR signal abnormalities, a relapse has been observed in about half of cases after a long-term follow-up over 10 years (Duffau, 2016). Yet, the patterns of relapse have not been specifically studied. This topic is very important due to the significant increase of the OS in DLGG in recent decades. Here, we reviewed the large spectrum of recurrence patterns of surgically resected DLGG, with several unusual scenarios beyond the classical slow local re-growth. Indeed, we showed a large heterogeneity in the spatial and temporal modalities of post-operative relapse in DLGG, with very diffuse, ipsi- or bilateral gliomatosis-like progression, multicentric recurrence with emergence of remote low-grade or high-grade glioma, leptomeningeal dissemination, acute (early or delayed) local MT or bulky relapse into the operating cavity.

Because the underlying pathophysiology is still unclear, and due to the rarity of these atypical re-progression patterns, further multicenter studies should be considered to better understand the mechanisms subserving these distinct patterns, especially with regard to molecular perspectives. The ultimate aim would be to predict not only when but also how DLGG will recur, in order to adapt multistage therapeutic management to each patient and to each pattern of relapse over the years. In practice, these findings plead in favor of a rigorous clinical, neurocognitive and radiological surveillance throughout life.

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Conflict of interest

None.

Authorship

Conception and design: Duffau. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Duffau. Study supervision: Duffau.

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