# Leptomeningeal spread in glioblastoma: diagnostic and therapeutic challenges

Cristina Birzu, Suzanne Tran, Franck Bielle, Mehdi Touat, Karima Mokhtari, Nadia Younan, Dimitri Psimaras, Khe Hoang-xuan, Marc Sanson, Jean-yves Delattre, et al.

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Birzu C[1], Tran S[2], Bielle F[2], Touat M[1], Mokhtari K[2], Younan N [1], Psimaras D[1], Hoang-Xuan K[1], Sanson M[1], Delattre JY[1], Idbaih A[1]

1. Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, F-75013, Paris, France

2. Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neuropathologie-Escourolle, F-75013, Paris, France

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## Introduction

Glioblastoma (GBM) is the most common and the most aggressive primary malignant brain tumor in adults.[1–3] Its annual incidence is close to 3 per 100,000 habitants per year. The treatment of newly diagnosed GBM patients relies on maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide chemotherapy [4]. Despite the intensive therapeutic regimen, the prognosis of GBM patients remains poor with a median overall survival below 18 months and a five-year survival rate of 5.6%[2].

The propensity of GBM to metastasize to cerebrospinal fluid (CSF) flow stream inducing GBM leptomeningeal spread (LMS) was firstly described in 1931[5]. LMS results from spreading of tumor cells from brain parenchyma to leptomeninges and CSF and is one of the most severe complications of GBM. Other severe complications of GBM include: (i) intratumor hemorrhage, (ii) status epilepticus and, (iii) hydrocephalus. As the prognosis of GBM patients improves, LMS becomes a more frequent clinical issue in neuro-oncology[1,6,7].

Considered initially as a rare complication in gliomas,[8] the incidence of LMS seems above the estimated rate of 4% reaching 25% on postmortem neuropathological studies [1,5,6,9,10] In case of LMS, the median overall survival of GBM patients varies between 2-5 months [1,6,7,11,12]. No risk factor has been clearly demonstrated although multiple factors have been suggested: (i) age, (ii) histologic features, (iii) molecular alterations, (iv) anatomical tumor site and, (iv) therapeutic interventions (*e.g.* surgical opening of the ventricles or antiangiogenic therapies)[1,6,13–16].

Diagnosis of LMS in GBM patients is challenging. The sensitivity of classical diagnostic investigations (i.e. MRI and cytological CSF analysis) remains low, failing identification of tumor CSF spread most of the time [17,18].

There is no standard of care treatment for LMS in GBM patients even though multiple groups have proposed several therapeutic options (e.g. methotrexate, cytarabine, thiotepa and/or, ACNU) with limited efficacy so far. [1,6,7,11,15,19–21] Interestingly, the treatment with intrathecal chimeric antigen receptor T cells has demonstrated dramatic efficacy in a single patient[22]. The uprising molecular targeted therapies and immunotherapies supports further exploration of the molecular landscape of CSF circulating GBM cells [23–26].

Diagnostic and therapeutic challenges raised by LMS in GBM patients will be presented and discussed in the current review.

## Method

We conducted a survey, from 01/01/1989 to 31/12/2019, in PubMed Database and Scopus-EMBASE using the following combination of terms connected by Boolean operators: (glioma OR high grade glioma OR glioblastoma) AND (meningeal OR leptomeningeal OR leptomeningeal dissemination OR meningeal gliomatosis OR leptomeningeal gliomatosis OR meningeal metastasis OR CSF dissemination) to identify relevant studies related to LMS and glioma.

Our search retrieved 2043 articles. We have excluded: (i) duplicate articles, (ii) articles in other language than English and French and, (iii) irrelevant articles –i.e. primary meningeal

gliomatosis, pediatric tumors. Eighty-five full text articles were selected. Based on this first selection and linked-list of references, additional articles were identified and included in our review. Overall, 156 articles were identified as relevant to the topic. The research algorithm is schematized in Figure 1.

## Epidemiology

LMS in high-grade gliomas was reported by several authors (Table 1). In a series of 600 GBM, Vertosick et al estimated the incidence rate of symptomatic LMS at 2% [1,6,7,10,11,27–32] . This incidence rate is probably underestimated due to undiagnosed and asymptomatic cases. Indeed, in autopsy studies LMS was identified in up to 25% of high grade glioma patients[1,10,15,27,28,33].

## Pathogenesis

Few is known about the pathogenesis of LMS. CSF dissemination seems to follow two patterns: (i) intense CSF seeding with limited tumor progression at initial tumor site or, (ii) minimal CSF seeding with massive tumor progression at initial location [1,5,10,34].

GBM cells migrate from the initial tumor site along brain vessels to subpial, subarachnoid and subependymal spaces (figure 2a) [5,10,35,36]. The leptomeningeal seeding from cortical areas is preceded by subpial spread as an intermediary step [5,10,17,35]. During this migratory process, GBM cells secrete multiple proteases degrading the extracellular matrix (ECM) (e.g. MMP 1, 2, 7, 9, 14, and 19 with a critical role of MMP 2 and 9) to create a moving space [37–42] and express multiple adhesion-migration proteins (e.g. glycosylated chondroitin sulfate proteoglycans, fibronectin, fascin and, integrins)[35,39,41,43]. Both molecule classes, working synergistically with cytoskeleton, allow tumor cells migration toward leptomeninges and CSF[5,18,28,30,35,39,41,43–45].

Furthermore in a mouse model prolonged VEGF inhibition converted tumor cells phenotype to invasive/mesenchymal leading to tumor invasion through perivascular and subpial spaces[46]. Multiple proteins including FGF, IGFBP2, MMP2, Podoplanin, Fascin, MET, TGF-B and, IL8 are involved in this process but further insight is needed[44,46–50].

The role of the glioma stem cell like cells and their cross talk with microenvironment cells in tumor cell migration remains poorly understood[41,45]. Translational and preclinical research are shedding light on molecular and cellular mechanisms of this phenomenon and its implication in invasiveness potential of GBM and in LMS development [26,37,51–53].

## Clinical presentation

Two thirds of GBM patients develop LMS within the two first years after diagnosis [1,7,11,20,28,30,33,54]. The median delay from initial diagnosis of GBM to clinico-radiological evidences of LMS varies from 5 to 16.4 months [1,5–7,10,11,15,20,28,30,33,55–58]. This delay is shorter in specific tumor location including pineal, spinal, periventricular and infratentorial [12,15,59–66].

Clinical presentation of LMS is heterogeneous, from asymptomatic to severely symptomatic disease[1,6,11,12,15,29,31,67]. Usually the onset and the worsening of symptoms are progressive, acute presentation is exceptional [5,12,27,36,68–70].

LMS patients can suffer from cranial nerves palsies, increased intracranial pressure syndrome, hydrocephalus, meningism, and/or focal neurological deficits [1,7,15,20,33,71–76].

Seizures frequency does not seem to increase during LMS development [77]. Confusion and generalized cognitive decline are the most common features of LMS in elderly GBM patients [15,78,79]. Although rare, aseptic fever, central neurogenic hyperventilation and cardiac arrest are reported [5,11,12,70,80,,]

Intractable vomiting may be an early symptom of CSF seeding to the fourth ventricle [81]. Cranial nerves deficits including 2nd, 3th, 4th, 6th and/or 7th, are observed in 6 % of cases [8,78]. The 4th and 7th are the most frequently involved [78,82]. Once installed, cranial nerve palsies are often irreversible [5,27].

Progressive paraplegia, [9,27,36,69,73,83,84] sphincters incontinence[1,11,36,55,80,84] and spinal ataxia [20,29,80] were described when the spinal cord or cauda equina are involved [9,29,30,33,69,73,85,86]. Isolated symptoms such as paresthesia, ataxia, back pain and leg or shoulder pain are rare [2729,87,88]. Radicular pain has been described with various topography: the upper limbs, interscapular [89] thoracic or lumbar level as well as sciatalgia [1,5,11,15,20,33,55,90].

Noteworthy, although LMS may manifest as communicating hydrocephalus [33], only 25-40 % of LMS present this complication [75,91].

**Risk factors**

A number of risk factors of LMS have been investigated in GBM patients. Young age (around 35 to 45 years), brain location, male gender, long survival after initial diagnosis and tumor volume seem to be associated with a greater risk of LMS in GBM patients [1,6,27,78].

The initial tumor location seems to be of importance. Indeed, infratentorial location (in 45 % to 100 % of cases) [1,5,10,13,62,63] and GBM of the pineal region [59] are associated with a higher frequency of LMS. The spatial proximity to ventricles and the tumor size were considered as risk factor of LMS but existing data are conflicting [1,6,7,11]. Indeed, invasive behavior of tumor cells and the environment of the subventricular zone (SVZ) have been pinpointed [1,14,15,30,85,92,93].

Ventricular opening during surgery and repeated surgeries, even more in patients treated with radiotherapy or chemotherapy[5,89] have been proposed as risk factors of LMS [15,65,94,95]. However, none has been clearly validated [1,14,29,75,92–97] and prophylactic radiotherapy in these cases does not bring supplementary benefit[98]. Persistence of preoperative leptomeningeal enhancement after initial surgical resection was also correlated with a higher LMS incidence in recurrence[99].

Hydrocephalus with subsequent ependymal fissuring has also been suggested as a potential but not formally validated risk factor [89,100].

Histological and molecular characteristics of initial tumor were also investigated. Astrocytic phenotype, high Ki67/Mib1 expression index [1,29,60,85,101,102] and GFAP loss of expression either at initial diagnosis[10] or at recurrence [28,29] were correlated with higher risk of LMS. Epithelioid GBM [26,103,104] and GBM with a neuronal component or PNET-like GBM [56,74] disseminate more frequently to CSF.

Some molecular alterations have been also suggested as risk factors of LMS[85]. Gain of 1p36 [105], *PTEN* mutation[102,106] and *PIK3CA* mutations [107] seem to predispose to meningeal seeding [102,105,106]. O6-methylguanine-DNA methyltransferase promoter methylation was also proposed as risk factor by isolated studies[65,108] The suspected mechanisms is increased survival in MGMT promoter methylation GBM patients giving time to tumor cells to reach

CSF[65]. This was not confirmed by larger studies [11,109] and up to date, no molecular signature has been validated as risk factor of LMS in high grade glioma.

Antiangiogenic therapies (VEGF and COX2 inhibitors) have been suggested as promoters of distant recurrence including LMS[44,48] but available data are conflicting. Further studies are needed [1,49,50,110].

**Diagnostic approach**

*Imaging*

Currently, the standard exam for LMS diagnosis is contrast MRI with a sensitivity reported between 90% and 100% for brain [1,6,11,99,111–114] and 56-95 % for spinal LMS in symptomatic patients[1,6,11,114]. Radiological screening of the neuraxis is required in GBM patients with suspected LMS symptoms [71,111,115].

However, the benefit of neuraxis screening for GBM patients without LMS symptoms remains unclear. This could be considered since the presentation can be asymptomatic and LMS can occur with stable disease at initial tumor site particularly in subgroups of high risk of LMS[1,29,56,59,63,103,111]. Exceptional cases of asymptomatic LMS like-leptomeningeal enhancement on MRI were reported in the setting of radio induced pseudo progression [116].

Typically LMS appears on MRI as linear and/or nodular foci with high signal intensity on T2 weighted images, low signal intensity on T1 weighted images and enhanced after gadolinium injection[111]. MRI LMS pattern was proposed using enhancement characteristics: (i) nodular -type Ia, fig. 4-, (ii) diffuse -Ib, fig. 5- in the subarachnoid space[18,34] and, (iii) subependymal dissemination -type II fig. 4,6- is also described regardless CSF cytology status [34] Mixed pattern is also possible – figure 6[1,34]. Distribution of LMS varies involving commonly the anterior parts of brain stem and cranial nerves [101]. Still, the expanded use of antiangiogenic agents seems to modify this pattern making it more difficult to distinguish, in these cases a potential interest of contrast enhanced FLAIR sequences can be discussed [34,55].

In intracranial LMS, brain MRI can show multiple aspects: (i) nodular enhancement 38% -subarachnoid or ventricular fig 4- and, (ii) pial enhancement 47 % -focal or diffuse- [1,11,34]. Nerve roots enhancement can be seen in some cases (57%) as well as cranial nerve infiltration (11-19%)[1,34,78]. Exceptional presentation mimicking chronic subdural hematoma or empyema have been reported[117,118].

Spinal LMS has been reported to be more frequently in lower thoracic, upper lumbar (most often posterior)[36,101], lumbosacral regions, cauda equina and dural sac [36]. 31% of lesions are described on cervical level, 52 % on thoracic level and 41% at lumbar level (fig 2b).[1,34,101,111] Cauda equina and conus medullaris were involved in up to 38% of cases [1,111].

Intraoperative detection of LMS using 5-aminolevulinic acid (5-ALA) was reported as useful in anaplastic astrocytoma (histone K27M mutated)[9] but its benefit is inconsistent[66]. Nuclear imaging detecting hyper metabolic foci using F-FDG [22,23] or TSPO(translocator protein) with F-GE-180 [119,120] can be helpful.

*CSF study*

CSF analysis is often negative for detection of tumor cells, only 25-45% are positive after a first assay[1,11,30,65]. Repeated lumbar puncture increases the diagnostic sensitivity to 86% with 3 consecutive lumbar punctures [65,71,78] and to 93% with more than 3 lumbar

punctures [6]. Nevertheless, even in cases of radiologically confirmed LMS, CSF cytological results were positive in only 4–75% of cases making an abnormal neuropathological CSF study sufficient but not necessary for diagnosis of LMS in gliomas[1,6,11,28,65,85]. Indirect aspects can be observed as high intracranial pressure (>15 cm H2O ), high proteins level (>50-100 mg/dL) with or without low glucose, high lactate with an acellular aspect [15,85,121] although a mild pleocytosis with presence of macrophages has been described [94].

On cytological exam, GBM cells were noted most often to be singly dispersed in the CSF (fig 2c). The main challenge is their distinction from monocytes [18].

The input of liquid biopsies in diagnosis and monitoring of LMS in GBM patients, has been explored with increasing interest over the last years[122–124]. Collecting and analyzing tumor components floating in CSF (i.e. circulating tumor cells, CTCs; cell-free tumor DNA (ct DNA) RNAs, (ctRNA, miR and exosomes) may help noninvasive diagnosis of CNS tumors and heighten the sensitivity in LMS detection [122,123,125]. CTCs and ctDNA seem to be of clinical interest [126]. In systemic malignancies CSF CTC assay has a reported sensitivity between 81-100% and a specificity of 85-97%. However, for non-epithelial malignancies such as GBM, the appropriate detection technique needs to be established [122,126].

As for the CSF ctDNA, analysis can be particular useful for detection of clonal mutations (BRAF V600E, IDH1, IDH2, TERT promoter, ATRX and TP53 mutations, EGFR amplification,) [23,122,123,127]. Noteworthy, although there is a clear correlation between CSF ctDNA and survival, the CSF detection of ctDNA does not systematically mean LMS, its clinical value in this context remains to be established[122].

**Therapeutic approach**

In most cases, LMS in glioma patients is considered an untreatable end stage complication of the disease[34]. There is no consensus nor standard of care regarding treatments[81]. Multiple treatment modalities, such as intrathecal chemotherapeutics and radiation therapy, seem to have improved median survival from 4–6 weeks to 3–6 months in high grade gliomas [128] Survival of LMS GBM patients in studies is reported at 0.2-9.7 months with a mean of 4.7 months[1,28,129].

Progression of the disease or treatment related complications (as hemorrhage[130], infections[20,33] after intrathecal administrated treatment or ventriculoperitoneal shunting[20,131,132]) may sometimes contribute to the fatal outcome [82,130].

*Surgery*

Because of the multifocal character of LMS, surgical approach is not suitable [87]. Surgical resection of compressive nodular focal leptomeningeal lesions may provide symptomatic benefit without impacting survival [9,68,83]. Another use for surgery in LMS is placement of a ventriculo-peritoneal (VP) shunt in case of hydrocephalus [11,14,20,72,131,133]. This seems to be necessary in up 20-30% of patients [11]. The main complications are shunt occlusion due to high fibrinogen CSF concentration[132,134], VP valve malfunction[134], hemorrhage, meningitis [20,131,134] as well as extracranial dissemination in peritoneal cavity [111,134]. The latter is exceedingly rare, although postmortem diagnosis in asymptomatic patients is possible[111,134]. In case of shunt occlusion, the use of urokinase can be considered [132] and careful monitoring should be ensured[20,131].

*Radiotherapy*

Palliative radiation therapy is the most commonly used treatment modality. Doses between 20 to 40 Gy are usually delivered allowing a good symptomatic control, especially for pain relief [27,68,87,115,135], compressive symptomatology [83,87] or intractable vomiting due to seeding to fourth ventricle[81]. Although focal LMS from systemic cancers is sometimes treated by stereotactic radiosurgery, its use in GBM LMS is rarely reported[1,6,60]. The clinical benefit is limited in terms of neurological deficit recovery or survival when administered alone [27,33,68,84,87,136] and it improves slightly when added to surgery [27,68,69]. Isolated trials of radiolabeled monoclonal antibodies failed to improve significantly the survival of the LMS patients[137].

*Pharmacological treatment*

Multiple chemotherapeutic regimens have been investigated : (i) TMZ alone or combined with BCNU[7] or CCNU[55], (ii) Thiotepa alone[57,58] or combined with Procarbazine[20,58,64], (iii) Methotrexate[6,15,20,57,138], (iv) Cytarabine[19,57,129,139,140], (v) Topotecan or Irinotecan[15,141,142] and, (vi) Platinum based agents with or without Etoposide[56,74]. Drug administration was either oral[7], intravenous[1,6,11,15,64,143] intrathecal via Ommaya reservoir/ lumbar puncture[6,11,19,21,57,58,139,141,142] or subcutaneous port [138] or combined [1,6,7,11,20,110].

Antiangiogenic drugs (e.g. bevacizumab) alone[1,44,118,143] or combined with cytotoxic agents (e.g. irinotecan) were used with inconsistent clinical benefit [15,55,64,85,110,135,144]. Concurrent radio-chemotherapy can be proposed in selected cases eventually in association with antiangiogenic agents[15,31,55,135].

Targeted therapy can be considered in selected cases (Table 2) as the MAPK pathway inhibitors (i.e. BRAF and/or MEK inhibitor) in $BRAF^{V600E}$ mutant GBM [23]. Dramatic clinical and radiological response were reported with a survival benefit from 1 to 11 months [23–25,76]. This incites to extensive molecular testing [23–25].

As the brain-blood barrier breakdown is low and given the potential resistance mechanism, combined therapy with anti MEK should be considered from the start as it seems associated to longer survival [23,26] Radiotherapy can be discussed in order to increase survival while balancing the treatment benefit and its toxicity[145,146]. Due to the rarity of druggable targets in GBM, this option is available for about 6% of LMS GBM [11].

Immunotherapy

Immune checkpoint inhibitors were proposed in cases of high mutational load and with microsatellite instability, alone or in combination with molecular targeted therapies[23,147]. Nevertheless, there is no clear evidence of their efficacy in LMS [6,22,85,147]. The use of adoptive cell therapy seems to be of interest. The IL13R α2-targeted–CAR T cells (with 4-1BB as costimulatory domain and tCD19 as a marker for transduction) had encouraging results with no high-grade therapy-related side effects when used in a LMS of IDH wildtype, MGMT methylated GBM.[22,148] After repeated intraventricular administration of IL13BBζ–CAR T cells a clinical and radiologic response was sustained up to 7.5 months [22]. Other constructs targeting EGFRvIII and HER2 having different costimulatory domains were explored but

their impact on LMS is not reported [149,150] . However, the difficulty in finding an adequate target, the immunosuppressive microenvironment as well as the consequent toxicities are the limitations of immunotherapy in GBM, including LMS patients[148].

Amongst perspectives, we count gene therapy using engineered mesenchymal stem cells transduced with herpes simplex virus-thymidine kinase gene (MSCtk) followed by systemic Ganciclovir (GCV) in a rat experimental leptomeningeal glioma model that seems to have encouraging results[151] and oncolytic viruses tested in transgenic mice inoculated with GBM cells[152]. Intrathecal immunoconjugates have also been advocated[90,153] as well as intratumoral/intrathecal targeted therapy[154].

The completed clinical trials (Table 3) explored the use of multiple intrathecal chemotherapies including topotecan, methotrexate and cytarabine in LMS. Although the safety profile was satisfactory, none of them showed significant improvement of LMS patients' survival[21,57,140,141]. Noteworthy, the ongoing disease-agnostic clinical trials (Table 4) allow LMS GBM patients inclusion. Nonetheless, their severe neurological impairment and their poor prognosis limit their enrollment.

Following the literature review, a management algorithm is proposed in fig 7.

Survival

LMS in primary malignant CNS tumor implies more aggressive behavior and a worse prognosis. Mean overall survival after diagnosis of treated LMS in high grade gliomas is 4.94 months (2-9 months) [1,6,7,27,44,60,86,143] . Exceptional OS up to 12 months were reported in cases with nodular LMS where the surgical resection was possible[83].

Among treated patients, the median OS was higher regardless chemotherapeutic regimen but the bias of delivering more intensive treatments in patients in better performance status should be taken into account [1,6,7,11,58,73,139,141]. Among studies, there seems to be a tendency of better survival for patients having received intrathecal chemotherapy (either Depocyt® or thiotepa) with mean survival up to 10 months [20,30]. A better survival seems associated with antiangiogenic (6-7.6 months mean survivals) [11,55,143] and molecular targeted therapy when appropriate [11,24,25]. Nevertheless, all this data needs to be validated in prospective trials.

Despite significant efforts to standardize the response assessment in LMS, this has been proven challenging[155] and it varies according to clinical trial outcome measures. The main criteria for assessing objective response in LMS treatments are the improvement of CSF cytology[140,141] and radiological decrease of LMS extent[1,6,7,11,15].

Up to 50% of LMS patients are treated only by best supportive care and considering the symptoms severity, we need to underline importance of palliative care guidelines in LMS management [156]

Prognostic factors

Although the reserved prognosis of LMS is well known, data on the prognostic factors are limited. The interval time from the initial glioma diagnosis to the LMS diagnosis is a potential prognostic factor [7] as well as Karnofsky Performance Status [30,82]. Males seem to

have shorter progression free survival  though the impact on overall survival does not seem significant [30]. Noteworthy, the extent of LMS does not seem to have a predictive value[1].

## Conclusion

Data on LMS in GBM patients remain scarce while it becomes more common in neuro-oncology clinics. The main problems are the lack of reliable early diagnostic tools and consensual standard of care.

Based on our review of the literature, multimodal treatment of LMS including surgery, radiotherapy, chemotherapy and/or best supportive care is a suitable approach to be discussed during multidisciplinary brain tumor board.

Interestingly, given the advances in glioma therapeutics including molecular targeted therapies and immunotherapies the landscape of LMS treatment is evolving. However, investigations of these innovative treatments remains limited in the setting of LMS and need further studies. Given the dismal prognosis and increasing incidence of this GBM complication, identification of risk factors, biomarkers and efficient therapeutic options in large prospective studies and clinical trials are warranted.

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