

Case Report

# Spinal Intradural Intramedullary Dissemination in the Absence of Intracranial Relapse of a Previously Radically Treated Temporal Lobe Glioblastoma Multiforme

Lucas Serrano<sup>a</sup> Eleftherios Archavlis<sup>a</sup> Elke Januschek<sup>b</sup>  
Pavel Timofeev<sup>b</sup> Peter Ulrich<sup>b</sup>

<sup>a</sup>Department of Neurosurgery, Mainz University Hospital, Mainz, Germany; <sup>b</sup>Department of Neurosurgery, Sana Klinikum Offenbach, Offenbach, Germany

## Keywords

Spinal intradural intramedullary dissemination · Temporal lobe glioblastoma multiforme

## Abstract

Intracranial glioblastoma multiforme (GBM) constitutes the most frequent and unfortunately aggressive primary central nervous system malignancy. Despite the high tendency of these tumors to show local relapse within the brain after primary therapy, dissemination into the spinal axis is an infrequent event. If spinal metastases occur they are leptomeningeal in the vast majority of cases and always in the context of intracranial progressive disease. Spinal intramedullary metastases of intracranial GBM have rarely been described to date. We report the unique case of a young woman with subacute progressive paraparesis due to spinal intramedullary metastases of a temporal lobe GBM despite the remarkable absence of intracranial tumor relapse. The patient had undergone gross total resection of a left temporal GBM in contact with the ventricles and cisternal space followed by radio- and chemotherapy 13 months before. At the moment of diagnosis of spinal intramedullary metastases, there were no signs of intracranial tumor recurrence as revealed by MRI scans. Since a high level of suspicion may be needed to detect this rare evolution of intracranial GBM and other differ-

ential diagnoses must be ruled out at presentation, we discuss the important features of this case regarding clinical manifestation, diagnosis, surgery, and management. Furthermore, we mention possible factors that may have contributed to the development of these metastases in the context of intracranial remission.

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## Introduction

Glioblastoma multiforme (GBM) constitutes the most frequent and aggressive primary intracranial malignancy, comprehending 12–20% of adult intracranial tumors [1]. Despite an aggressive therapy, patients with GBM show a local relapse in almost all cases and they die of progressive intracranial disease [2]. However, symptomatic extracranial metastases within the spinal axis or in other organs are unusual. If spinal metastases occur, they are usually leptomeningeal and in the context of an advanced intracranial involvement, being intramedullary localization an extremely rare event [3–6]. In the present article, we report the rare case of a young female patient who developed spinal intradural intramedullary metastases of an intracranial GBM while there was no evidence of intracranial relapse. We present the clinical, diagnostic and surgical features of this case and provide possible explanations for the development of intramedullary GBM metastases in the absence of intracranial progression.

## Case Report

A 33-year-old woman presented at the emergency department with a subacute progressive bilateral leg weakness. The neurological examination revealed a severe paraparesis, as well as hypesthesia of both lower limbs in the absence of sphincter incontinence or radicular pain. Reflexes were hyperactive in both legs, with no evidence of clonus or Babinski sign. The patient had been diagnosed 13 months before with a temporal lobe GBM (Fig. 1a). She had undergone surgical gross total tumor resection and postoperative MRI scans had revealed a very small residual contrast-enhancing abnormality (Fig. 1b). Postoperatively, the patient had no other remarkable neurological deficits besides a light remaining right hemiparesis and had undergone concomitant radio- and chemotherapy followed by 6 cycles of adjuvant temozolomide. Nevertheless, the doses of temozolomide had to be reduced due to a severe thrombocytopenia developed by the patient during the treatment.

Brain MRI at the time of consultation due to paraparesis showed no evidence of a local intracranial recurrence (Fig. 1c). However, MRI of the spine demonstrated a homogeneous contrast-enhancing mass within the spinal canal at the Th8/9 level causing significant spinal cord compression (Fig. 2). A lumbar puncture was performed and cytological examination of the cerebrospinal fluid (CSF) did not reveal the presence of neoplastic cells.

Due to the spinal cord compression and progressive paraparesis, we suggested surgery with the aim of decompressing the spinal cord and if possible remove the tumor. Therefore, we performed a decompressive laminectomy at the Th8/9 level. After opening the dural sack, an intradural intramedullary high vascularized infiltrating tumor was identified (Fig. 3a, b). Due to its adherent and infiltrating pattern with no recognizable edges to the normal tissue, it was unreasonable to attempt a radical tumor excision so we carefully performed a biopsy and interposed a dural graft to expand the spinal canal, therefore reducing the pressure against the spinal cord (Fig. 3c, d).

Unfortunately, neurological deficits did not improve during the postoperative follow-up and the patient refused to undergo further oncologic therapies. She underwent best supportive care and died 5 months later due to complications of pneumonia acquired in the context of a highly debilitated general state of health.

## Discussion

Drop metastases refer to neoplasm dissemination following the CSF circulation [7]. This type of spread constitutes a not so unusual feature for some intracranial neoplasms such as ependymoma, medulloblastoma as well as germinal and pineal tumors [8]. Nevertheless, symptomatic metastases within the spinal axis are rare events in patients with intracranial GBM and if they occur their distribution follows a leptomeningeal fashion in the great majority of cases [3–6]. Despite evidence from autopsy series suggesting that approximately 25% of patients with supratentorial and possibly up to 60% infratentorial GBM could have spinal leptomeningeal spread, even these metastases from primary GBM rarely become symptomatic [9, 10]. In recent large series, clinically relevant spinal drop metastases are found only in approximately 1 or 2% of GBM patients and consisted mostly of primary meningeal involvement with secondary compression and infiltration in some cases of neural structures [5, 11, 12]. Intramedullary metastases, such as the one described here, are rare in the literature [6, 13, 14].

Furthermore, drop metastases of GBM usually develop in the context of an advanced disease and most of the patients diagnosed with clinically relevant spinal metastases of GBM present simultaneously a multicentric pattern of tumor relapse in cerebral MRI scans [3–6]. In a report of 9 patients from Tinchon et al. [5], this correlation was evidenced in all the examined cases. However, in our patient, the development of spinal intramedullary metastases was clinically evidenced 13 months after the first diagnosis of intracranial GBM and there was no evidence of an intracranial relapse at the time of presentation of these metastases (Fig. 1c).

After a thorough review of the literature, only few cases of adult patients with cerebral GBM have been reported who developed symptomatic spine compression referable to leptomeningeal dissemination without clinical or radiological evidence of primary intracranial recurrence [15, 16]. However, our case constitutes, to our knowledge, the second case of spinal intramedullary intradural metastases in patients with GBM in the context of a controlled intracranial disease and the first one after temozolamide has been established as a standard adjuvant therapy for newly diagnosed GBM [17].

Taking into account the rarity of this event and since neuroimaging scans cannot always determine with certainty the intra- or extramedullary nature of large spinal tumors, other etiologies such as meningiomas and neurinomas must be ruled out in case of isolated spinal cord masses in a patient having been treated for GBM. It must be remarked that genetic syndromes like type 2 neurofibromatosis combine the possible occurrence of gliomas, neurinomas and meningiomas in the same patient [18]. In addition, Wagner et al. [19] reported the case of spinal cord schwannomas mimicking drop metastases in a patient previously diagnosed with intramedullary ependymoma. In the case we present, MRI images were inconclusive to define whether the spinal tumor was located intra- or extramedullary. Moreover, the homogeneous contrast enhancement suggested the possibility that this tumor could correspond to a neurinoma or meningioma. Since cytological examination of the CSF was also unsuccessful to obtain a diagnosis, we considered surgery a reasonable strategy to decom-

press the spinal cord as well as to assess the feasibility of tumor removal or otherwise at least obtain a histological probe.

Regarding the mechanisms of occurrence of intramedullary spinal metastases observed in our patient, we may speculate that the contact and involvement of lateral ventricles and cisternal space shown by the original intracranial GBM could eventually have contributed to the dissemination of GBM cells through the CSF. It has been proposed that traversing the ventricles at the time of biopsy surgery for GBM could lead to CSF seeding and later development of spinal metastases especially if the primary tumor is located next to the ventricles. Albert et al. [20] reported the case of spinal metastases following a stereotaxic biopsy directed through the lateral ventricles and Birbilis et al. [4] present the case of a patient who developed spinal metastases after a stereotaxic biopsy of a pineal GBM next to the third ventricle. In a study of supratentorial gliomas in children, it was found that the incidence of CSF dissemination in cases of ventricular entry at operation was significantly increased [21]. Other authors suggest that ependymal invasion, fissuring of the ependyma due to hydrocephalus, and fragmentation of the tumor in contact with CSF are also risk factors for CSF dissemination [22]. In both patients with spinal metastases reported by Shah et al. [23], primary GBM were in close proximity to the ventricles and there was ependymal enhancement in 1 patient. During surgery, the ventricles had also been opened inadvertently in both patients and this could eventually have explained the rapid dissemination to the spine according to the authors. In this regard, Atalakis et al. [24] have suggested that treatment modalities to prevent CSF dissemination should be part of the management of patients with GBM showing contact to the ventricles. Although these strategies have not been validated in clinical trials, these authors have proposed stereotactic biopsy followed by cranial irradiation and delayed resection in selected patients suspected of high risk of CSF dissemination. Furthermore, they also suggest the use of intrathecal radiolabeled monoclonal antibodies to detect CSF spread if tumors show ventricular infiltration or ependymal enhancement in preoperative MRI.

Other authors have suggested that GBM with low astrocytic differentiation evidenced by a low glial fibrillary acidic protein expression may show an increased risk of developing leptomeningeal and intramedullary spinal metastases [14]. Nevertheless, this suggestion needs to be further validated before a general recommendation can be done regarding the performance of spinal metastasis screening in patients with GBM showing low glial fibrillary acidic protein expression.

However, we may remark that even if spread across the CSF could be considered a risk factor of spinal metastases in patients with GBM, as mentioned before, these metastases are distributed as expected along the leptomeninges. The pathogenesis of intramedullary intradural spinal metastases of GBM still constitutes an open issue.

Finally, we speculate that the difficulties in establishing a full-dose temozolomide-based chemotherapy in our patient due to severe thrombocytopenia could have been an additional predisposing factor for the development of spinal metastases in the context of nonprogressive intracranial disease. Locally acting therapies including surgery and radiotherapy could have led to an effective control of the brain tumor. However, in this scenario, systemic chemotherapy could have played a role in preventing or delaying spinal spread, considering that temozolomide has been reported to be an active agent in spinal GBM. Tseng et al. [25] published a case of primary intramedullary GBM of the spinal cord in which prolonged survival was achieved with temozolomide following surgical and radiation therapy. These authors stressed the important role that temozolomide could have played in delaying a relapse within the spinal cord. Additionally, other authors have reported the case of children with prima-

ry astrocytomas of the spinal cord, who achieved progression-free survival of 18 months after they have been treated with temozolomide-based chemotherapy [26].

## Conclusions

Intradural intramedullary metastases of intracranial GBM rarely occur in the context of a controlled brain disease. However, exceptional cases like the one we present exist and can carry devastating consequences for the patients, if they are not adverted immediately. Therefore, a high level of suspicion is needed to think of this possibility, particularly in patients with tumors located originally in contact with the ventricles or cisternal space as well as if they consult due to radicular pain, sensory and motor deficits distributed bilaterally, bowel and bladder incontinence or isolated mono- or multiple neuropathies. If a spinal tumor is observed in patients having been treated for GBM, obtaining a biopsy can be a safe method to secure the diagnosis as well as rule out other possible entities, i.e., meningiomas or neurinomas associated with a more favorable prognosis and management strategy. If the diagnosis of intramedullary spinal metastases of GBM is confirmed, several questions are still open regarding the pathogenesis and effective therapeutic options available for these patients, such as whether the dissemination of malignant cells is driven by CSF or whether temozolomide or other therapeutic agents could prevent the development of these metastases or would be effective once metastatic disease has occurred. Therefore, we expect that reporting similar cases in the future can provide concrete answers to these unresolved issues.

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## Statement of Ethics

The manuscript does not contain clinical studies or identity patient data. The authors have no ethical conflicts to disclose.

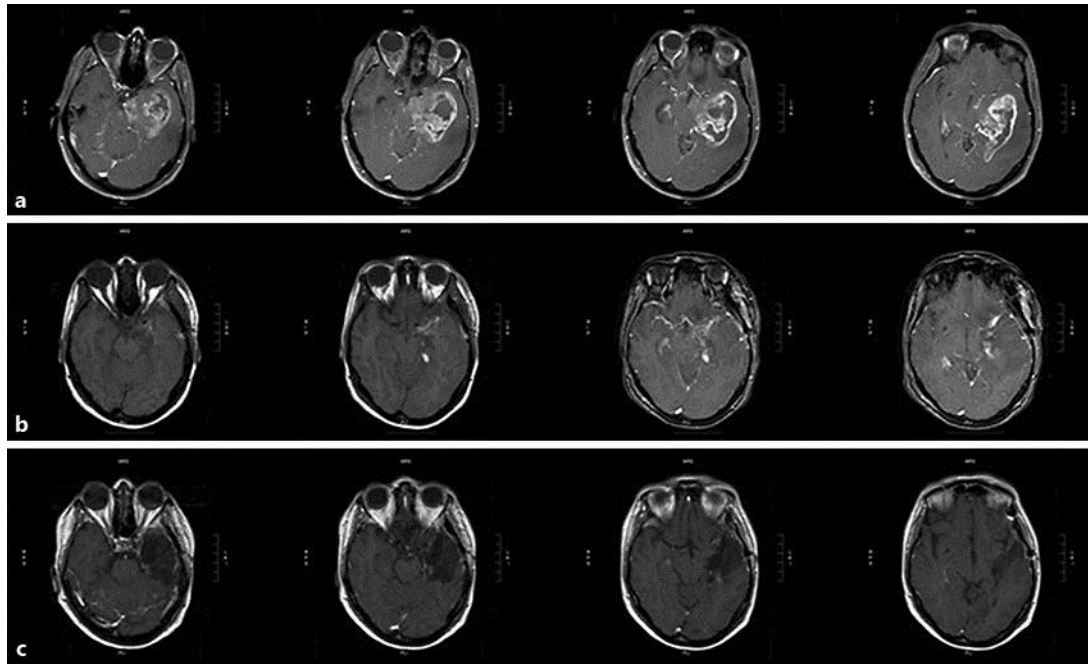
## Disclosure Statement

The authors declare that they have no conflict of interest.

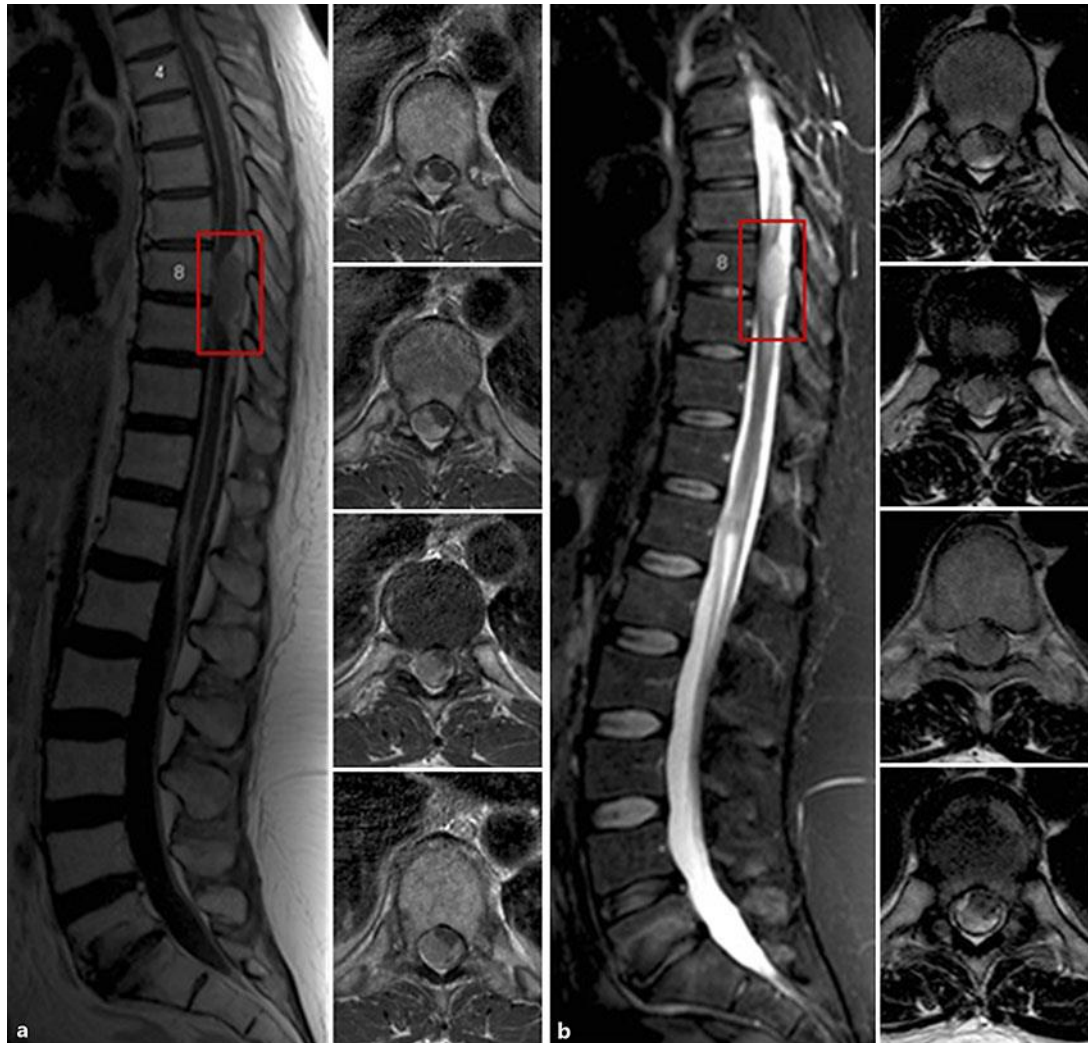
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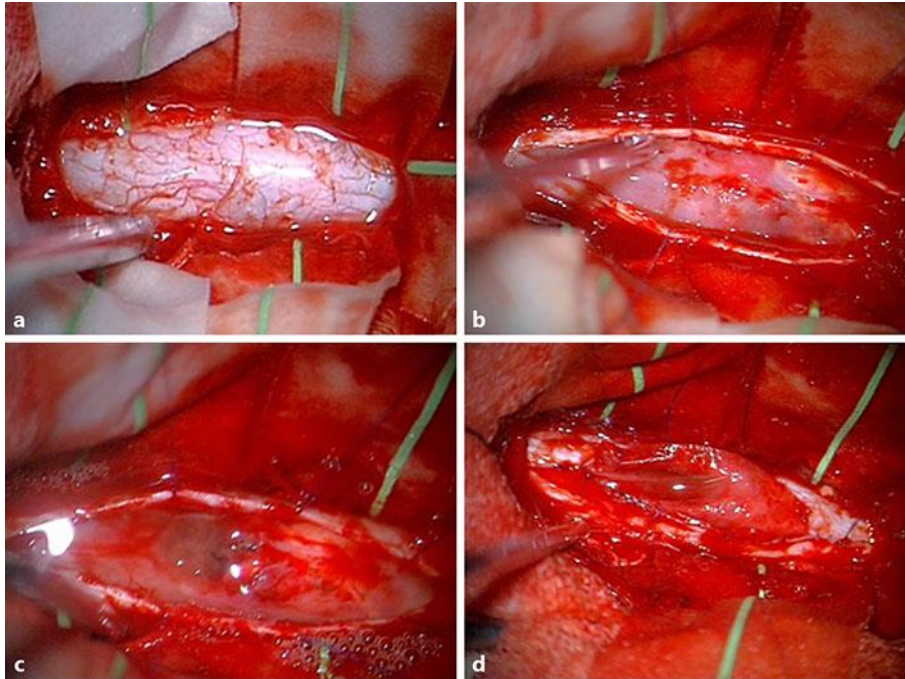


**Fig. 1.** Presurgical MRI images at the diagnosis of a left temporal lobe GBM, 13 months before the presentation of spinal metastases (a). Immediately after tumor removal, MRI scans show a minimal residual contrast-enhancing lesion on the left temporal lobe (b). Brain MRI performed 13 months later, at the moment of diagnosis of spinal intramedullary metastasis, showing no evidence of intracranial recurrence (c).



**Fig. 2.** Spinal MRI images obtained at the moment of presentation of progressive paraparesis 13 months after intracranial tumor removal followed by adjuvant therapy. T1 contrast-weighted images (a) and T2 sequences (b) reveal a large intraspinal tumor at the level of Th8/9, corresponding to intramedullary metastasis of temporal lobe GBM.





**Fig. 3.** Surgical approach to the spinal tumor through a laminectomy performed at the Th8/9 level. Spinal canal exposure revealed no macroscopic infiltration of the dura mater (**a**). After durotomy, an infiltrating, highly vascularized intradural intramedullary tumor lacking recognizable edges in regard to the normal tissue was observed (**b, c**). A biopsy was carefully performed and further histological examination confirmed the diagnosis of GBM metastasis (**c**). Duroplasty using a graft interposition was performed with the aim of widening the spinal canal and ameliorate the local compressive effect induced by the tumor (**d**).