Spinal Dissemination of Intracranial Glioblastoma in Bevacizumab Era: a Potential Bevacizumab-induced Mechanism

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1. INTRODUCTION
Spinal metastasis, a devastating neurologic complication of intracranial glioblastomas is not as uncommon as initially thought. It varies from 25% in supratentorial glioblastomas to 60% in infratentorial glioblastomas (1). However, autopsy series have shown a higher incidence than clinically expected of multifocal spread of malignant astrocytoma, so the incidence of spinal tumor spread may be underestimated (2).

The underlying pathogenesis spinal spread of high-grade gliomas is still unclear. Several studies attempt to elucidate the possible mechanisms raising important questions regarding the intrinsic biological features and anatomical location closely to the ventricular ependyma (1). But, in none of them a causal responsibility of Bevacizumab (BEV) was noted. Here, we report for the first time, a case of thoracic intramedullary metastases from a cerebral glioblastoma pre-treated with BEV. A critical and exhaustive review is provided.

Key words: Glioblastoma, lepto-meningeal seeding, bevacizumab.

2. CASE PRESENTATION
A, previously well, 63-year-old patient presented to our service with a 2 month history of headaches and language disorders. On admission, neurological exam revealed semantic paraphasia and slight right hemiparesis (4+/5). In a head CT (computed tomography), a left fronto-insular lesion with heterogenous contrast enhancement, highly consistent with a high-grade gliomas was seen. Because of the infiltrative nature of the tumor in the eloquent areas, we decided to try a new chemotherapy regimen using Bevacizumab concurrently to the Temozolomide. The patient signed the consent form and was subsequently treated with two monthly cycles of temozolomide (150mg/kg/d for 5 consecutive days) and two standard biweekly cycles of bevacizumab (10mg/kg). No adverse events were noted. The decrease of tumor size and peritumoral edema seen in the brain MRI of control (Fig) rendered the tumor amenable to radical surgery which was performed subsequently without sequelae (Fig). Histological examination of this specimen revealed a glioblastoma (WHO grade IV). Thereafter, the patient completed his radiotherapy concomitantly with temozolomide followed by adjuvant temozolomide. One month after completion of radiochemotherapy the patient experienced progressively ascending numbness on the left leg. As this symptom was ipsilaterally with the cerebral lesion, no attention was paid by local neurologist. After 3 weeks, he was referred to our department because of a motor deficit on that leg and appearance of same symptoms on the right leg leading in walking difficulties. Clinical examination revealed an inferior spastic paraparesis motor deficit of 2/5. An urgent MRI of brain and spine was performed revealing an intramedullary and non contrast-enhancing lesion at T5 thoracic level. A clear local control was noticed on the MRI of head. CCNU...
(Lomustine), a second cytotoxic agent was added to the adjuvant Temozolomide. Nevertheless, the clinical and neurological status of our patient deteriorated in the next three months and he died 6 months after LM metastasis diagnosis and 10 month after his initial radiological diagnosis.

3. DISCUSSION

Glioma dissemination and especially invasion are largely studied. There is growing data reporting the potential risk factors and possible mechanisms for spinal spread of high-grade gliomas. However, cerebral malignant gliomas rarely metastasize into the spinal cord. Different clinical patterns of spinal dissemination, lepto-meningeal, cord compression or intramedullary have been reported. Due to their rarity, there are limited cases upon which to base clear and definite conclusions. In the majority of them, glioma invasion seems to be related with some intrinsic biological features. We believe that other factors than intrinsic ones would play a role in spinal dissemination. Thus, several comments regarding these reports we believe are warranted.

In their recent article, Maslehaty et al (3) conclude that the hallmark of this process is the low GFAP expression (astrocytic differentiation). The study was designed as a case report with literature review. The authors suggested that patients with primary tumors showing low astrocytic differentiation (low GFAP expression) are in higher risk to develop earlier LM dissemination. However, their conclusion on such a small subpopulation creates a risk of over-interpreting apparent differences that may arise by chance and/or are not correlated with radiological, histological and genetic analyses. Furthermore, even though the primary intracranial tumor of their patient showed heterogeneous GFAP expression, he experienced lepto-meningeal progression.

Another important risk factor is considered the anatomical location of the first intracranial tumor. As we know, a particular relationship exists between glioblastoma multiforme and the subventricular zone (SVZ) neural stem cells region. Tumors in contact with the SVZ are most likely to be multifocal at diagnosis and to recur a distance from the initial lesion (4). Given that, one would wonder if that tumor location at the time of diagnosis of our high-grade glioma corresponded to the initial origin of tumor or to the migration of tumor cells from cortical/subcortical level.

Other biological features that seem to be significantly associated with spinal dissemination are PTEN gene mutation or high Ki67/Mib1 labelling index (5). Recently, high rate of EGFR gene amplification and protein expression were observed in disseminated pediatric low-grade gliomas compared to non-disseminated low-grade gliomas (6). EGFR activation up-regulates and induces translocation in vitro of FABP7 (BLBP), expressed by the radial glia and involved in glial guided neuronal migration. Inhibition of FABP7 expression suppressed EGF-induced glioma cell migration, suggesting that EGFR induced properties of glioblastoma is in part mediated by FABP7. FABP7 also co-localizes with GFAP and is preferentially expressed in cells with astrocytic features (7, 8, 9). In a previous report (10), we found the expression of FABP7 in large majority of astrocytic lineage with a correlation on invasive phenotype, strongly suggesting that EGFR activation induces FABP7 nuclear translocation and promotes migration.

So, we believe that additional studies further comparing the role of each of above mentioned biological markers in the pathogenesis of glioma dissemination are a real need. Any a-priori imbalance in these factors could skew study results in various directions.

No information about putative role of any kind of treatment in glioma spinal spread was provided in the actuarial literature. Bevacizumab (Avastin, BEV), an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, is found to be responsible for the increases in diffuse patterns of progression (11, 12, 13). Interestingly, our patient was treated in first-line and in neoadjuvant setting with BEV. The very earlier LM dissemination confirmed at our patient (3 months from BEV), led us in speculating that probably the present intramedullary dissemination was BEV related. This speculation is in line with the present opinion that treatment with BEV is associated with a higher incidence of distant or non-enhancing pattern of recurrence (11, 12, 13). Furthermore, this allows us to suggest that besides intrinsic and radiological characteristics, treatment with BEV may induce intramedullary dissemination. In this setting,
we report for the first time to our knowledge, a case of an intramedullary spinal metastasis BEV induced of a supratentorial glioblastoma. However, additional studies on the potential risk of spinal dissemination in malignant glioma treated with BEV in first-line or in recurrence are required.

Actually, we cannot exclude any of these hypotheses that would secondary have played its important role in developing intramedullary dissemination. On the other hand, the absence of any information on these factors, the lack of histology of spinal lesion, as well as the case report design represent the main limitations of our report.

4. CONCLUSION

In conclusion, we agree that determining a reliable and predictive biomarker and validating an effective therapy remains an unmeet need. It will be important to incorporate as much as possible biological and clinical data into future studies about spinal metastases from glioblastoma.

CONFLICT OF INTEREST: NONE DECLARED.

REFERENCES