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
Volved in glial guided neuronal migration. Inhibition of FABP7 (BLBP), expressed by the radial glia and up-regulates and induces translocation in vitro of disseminated low-grade gliomas (6). EGFR activation was significantly associated with spinal dissemination are compared to non-disseminated gliomas (6). EGFR activation increases in diffuse patterns of progression (11, 12). 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 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.

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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 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.

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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.

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