Editorial

Glioblastoma: an organ-confined disease?

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Gliomas are the most common primary malignant central nervous system (CNS) tumours, and glioblastoma (GB) is the most frequent and deadliest type. Median overall survival (OS) in patients with GB falls below fifteen months despite a maximal safe tumor resection followed by radiotherapy with concurrent and adjuvant temozolomide (TMZ) (1,2). In recent years, improvements in the understanding of the molecular biology of gliomas have led to the establishment of clearly differentiated molecular subtypes (3). The 5th edition of the World Health Organization (WHO) classification of CNS tumors, published in 2021, underscores the importance of the molecular profile for a proper denomination, particularly in gliomas (4). However, despite these advances, there have been no impactful therapeutic changes for patients with GB in the past 15 years. This is probably because GB is an infrequent cancer, with a complex biology and a dismal prognosis in terms of survival and neurologic functionality which, altogether, hinder the development of new therapies from its pre-clinical to its clinical phases (5).

Gliomas have been historically considered as an organ-confined disease due to the long-standing belief that extra-CNS metastases never occurred. Several factors may explain this, such as the existence of the blood-brain barrier (BBB), the limited capacity of GB cells to invade extracranial connective tissues and to grow in foreign organs, and the short OS of these patients (6,7). However, retrospective series and case reports of GB patients with extra-CNS metastases, challenged this assumption. In addition, the development of extra-CNS metastases in organ-transplant recipients from donor GB patients reinforced these observations and lead to hypothesize that immune-vigilance may be important to avoid GB dissemination (7-9). Although the real incidence of extra-CNS metastases in GB is unknown, it is estimated, from the available series, that they occur in 0.5–2% of patients. The true incidence is probably higher since GB metastases are usually clinically silent and extracranial imaging is not commonly performed in these patients (6,10). Extra-CNS metastases from GB more commonly occur in lymph nodes (LN), lungs, pleura, soft tissues, glands, liver, and bone (10). Coca-Pelaz *et al.* (11), recently conducted a systematic review of the literature published in the period 1944–2021, finding 174 cases of LN metastases from primary CNS tumors, with 52.8% being of glial origin. In this series other sites of distant metastases were bones (23%), lungs (11.5%) and non-cervical LN (11%). A fourth of the cases had been reported in the past 12 years, reflecting a growing interest for extra-CNS metastases from primary CNS tumors.

In a recent case series of GB extra-CNS metastases, Noch *et al.* (12) described 9 patients with GB and 1 patient with gliosarcoma diagnosed at the Memorial Sloan Kettering Cancer Center in the period 2003–2018. The median OS since initial diagnosis and since the diagnosis of extra-CNS metastases was 19.6 and 5.0 months, respectively. The most common site of extra-CNS metastases was bone, followed by LN, dura, liver, lung, and soft tissues. Matched next-

generation sequencing (NGS) analyses of the primary tumor and extra-CNS metastases revealed shared mutations in tumor suppressor genes, such as *TP53* as well as in *TERT*, *PTEN* and *CDKN2A/B*, with some of the mutations only detected in the metastases indicating clonal evolution, a well-known phenomenon in GB (13,14).

Among the few reports that have conducted genomic analyses in patients with GB and extra-CNS metastases, mutations in *TP53* have been the most frequently reported (6,12,15-19).

The mechanisms underlying the occurrence of extra-CNS metastases are not well understood. Anatomical mechanisms with local or regional post-surgical seeding may explain scalp or cervical LN metastases. Other reported mechanism is the occurrence of intraabdominal metastases after placement of a ventriculoperitoneal shunt (20).

Interestingly, in recent years, key conceptual ideas such as the inexistence of a lymphatic system in the CNS were disproved thanks to the discovery of meningeal lymphatic vessels as well as the presence of a glial-lymphatic—so called "glymphatic"—system that connects astrocytes with meningeal lymphatics draining to cervical LNs, thereby confirming a probable route of dissemination of GB cells to regional LN and beyond (21-23).

Finally, hematogenous dissemination is another mechanism that may explain many extra-CNS metastases, such as those in bone, lung, and other organs (7). Indeed, the seed and soil hypothesis originally described by Paget, was revisited in the past decades after the demonstration that circulating tumor cells (CTCs), and, especially, CTC clusters, were the main mechanism explaining hematogenous seeding in cancer (24,25). Particularly in GB, detection of CTCs in peripheral blood has been reported in up to 20% of patients, which could explain biologically the occurrence of extra-CNS dissemination in glioma (7).

BBB disruption after surgery and sarcomatous dedifferentiation were proposed as clinical risk factors for extra-CNS dissemination in GB, although the former was challenged by the lack of association between surgery and the detection of GB CTCs in peripheral blood (7,12).

In the current issue of *Translational Cancer Research*, Chai *et al.* (16), report the case of a 43-year-old male diagnosed of a left occipital GB, IDH-wildtype. After tumor resection the patient received radiation with concurrent and adjuvant TMZ. Six months after surgery a local recurrence occurred and only one month later a histologically confirmed metastatic mediastinal mass with bilateral pleural effusions, was diagnosed. NGS genomic analysis of the mediastinal mass revealed mutations in *TP53*, *CSMD3*, *PARP4* and *PTEN*, and a tumor mutational burden (TMB) of 8.667 Muts/Mb. Despite receiving a first cycle of TMZ and bevacizumab, the patient died from respiratory failure one month later. This case adds to the limited evidence of extracranial metastases from GB available in the literature, and to the very few studies that have undertaken genomic studies in metastases from gliomas. Coincident with prior reports, this patient was relatively young and had a rapid disease course after the diagnosis of metastases, which in most reports falls below 7 months (6,12,26). As in prior studies, mutations in tumor suppressor genes such as *TP53* were detected in the mediastinal LN metastasis of the current case. As this case and prior reports demonstrate, recurrent GB with extra-CNS metastases has very few treatment options. Exceptions to this rule are regional relapses such as those occurring in the dura and head and neck LN, or in oligometastatic bone metastases, which various reports have shown that may be subjected to local treatments achieving longer local and systemic controls (10,11,15,26). Considering that systemic therapy has not demonstrated to prolong OS in patients with recurrent GB, its management is even more complex in patients with extra-CNS metastases. In the current case, the patient did not benefit from a single cycle of TMZ + bevacizumab, probably due to his rapidly deteriorating condition. Other options that could be considered, are those commonly used in the second line setting of recurrent GB such as lomustine, fotemustine or irinotecan, alone or combined with bevacizumab (5). Despite the fact that EGFR-directed therapies did not demonstrate to benefit patients with glioma, it would be worth considering them for extra-CNS metastases, considering that 50–60% of GB are *EGFR*-amplified and up to 20% harbor the *EGFRvIII*, and both findings have been described in CTCs in peripheral blood from patients with GB (5,7). NGS studies of extra-CNS metastases may reveal potentially targetable genomic alterations that could offer new therapeutic options to these patients. Indeed, in this patient a relatively high TMB of 8.667 Muts/Mb was found in the LN metastasis, raising the question if immune checkpoint inhibitors could have been of any benefit, despite the negative results of immunotherapy trials in patients with GB. On the other hand, while the patient was not under corticosteroids, many patients with recurrent GB are under steroid therapy, which would reduce any potential benefit from immunotherapy for extra-CNS metastases (27,28).

Although screening for distant metastases is currently

not a standardized procedure in patients with GB, given the increasing awareness of their occurrence and the demonstration of the frequent presence of CTCs in the peripheral blood of patients with GB—which, in addition, it may be hypothesized to increase in the recurrent setting—it would be of interest to conduct diagnostic clinical trials of liquid biopsy using CTCs and/or circulating tumor DNA (ctDNA) coupled with imaging techniques such as ^{18}F-FDG-PET, PET-choline, or PET-methionine scans in order to stablish the true incidence of extra-CNS metastases and expand our knowledge on the systemic fingerprints of GB (7,29,30).

In summary, extra-CNS metastases are a rare but increasingly recognized manifestation of primary malignant CNS tumors. Tumor tissue NGS and liquid biopsy studies should be undertaken for diagnostic purposes and to offer potential therapeutic opportunities. In addition, molecular studies may aid in deciphering the biological nature and evolution of GB with extra-CNS dissemination. Clinical trials should also contemplate the enrollment of these patients to improve its currently dismal prognosis.

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