Uncommon Territory: The Clinical and Molecular Profile of Metastatic Gliomas

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Diffuse gliomas are masters of local invasion, effortlessly spreading throughout the central nervous system (CNS), reaching even the brainstem and cervical spine at late stages of the disease[1]. Paradoxically, despite extensive local spread, diffuse gliomas are systemically contained, with < 1% of primary tumors metastasizing outside of the CNS[2]. This observation is even more at odds with the fact that other solid tumors, such as lung, breast and skin cancers, frequently metastasize to the CNS. In fact, as much as 23.1% of small-cell lung cancers metastasize to the brain and the incidence of metastatic brain cancer vastly exceeds that of primary brain tumors in absolute numbers[3]. Several reasons may underlie these differences. Firstly, while leaky terminal capillaries permit the extravasation of circulating tumor cells into the brain, thick vascular basement membranes restrict the flow of tumor cells back into the blood[4]. Secondly, most patients with primary brain tumors succumb to the disease before it has a chance to spread. Furthermore, while primary brain tumors are diseases with mandatory reporting, there is no mandate to report metastatic spreading of those primary tumors (personal communication). In conclusion, the rarity of disease and the lack of systematic tracking, and consequentially, systematic studies, all contribute to the relative low consensus on the clinical and molecular properties of metastatic gliomas. It is in this context that the study by Jacobsen et al in this issue provides invaluable new insights[5].

Here, the authors describe their genomic analysis of an impressive cohort of n = 16 patients with extracranial metastases that were collected at the Copenhagen University Hospital in Denmark over a 20-year period of time. The cohort includes n = 6 patients with extra-cranial extensions and n = 10 patients with true extracranial metastasis to lymph nodes (n = 5), bone (n =2), neck (n =2) and liver (n = 1). Moreover, the authors noted an unusually high number of tumors demonstrating mesenchymal differentiation, a feature characteristic of the gliosarcoma histological subtype[5]. These observations are corroborated by a number of earlier studies suggesting that gliosarcomas have a higher propensity to metastasize[7].

Applying exome sequencing to their tumor samples, the authors show that the metastatic tumors harbor the same oncogenic drivers that were observed in the patient-matched primary tumors, including well-known driver mutations in *IDH1*, *PTEN* and the *TERT* promoter. Pathognomonic aneuploidies, such as the 1p/19q codeletion and the combined gain of chromosome 7 and loss of 10 were also preserved between the primary and metastatic lesion. In some cases, biomarkers of tumor progression were uniquely found in the metastatic lesion. For example, in two cases the authors describe a deletion of the *CDKN2A* tumor suppressor gene unique to the metastasis, suggesting an aggressive dedifferentiation of the tumor had occurred after initial diagnosis. Array-based DNA methylation classification and RNA sequencing both demonstrated a shift to mesenchymal subtypes, corroborating the predominance of the gliosarcoma histology in metastatic tumors. An in-depth analysis of individual DNA methylation changes between timepoints indicated an overall hypomethylation at metastasis, which is in line with reports demonstrating similar DNA methylation changes associated with tumor progression[8].

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