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Mesenchymal-type genetic mutations are likely pre-requisite for glioblastoma multiforme to metastasize outside the central nervous system: an original case series and systematic review of the literature

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Abstract

Background: Glioblastoma multiforme (GBM) is the most aggressive and prevalent type of malignant brain tumor, yet they metastasize outside of the central nervous system (CNS) in 0.4% of all cases. Little is known about what enables this subset of GBMs to take root outside the CNS, but genetic mutations likely play a role.

Methods: We conducted a PRISMA-compliant systematic review of metastatic GBM wherein we reviewed 3579 search results and 1080 abstracts, ultimately analyzing data from 139 studies and 211 unique patients. Additionally, we describe four cases of patients with pathologically confirmed GBM metastases outside the CNS treated at our institution.

Results: We found that metastases were discovered near previous surgical sites in at least 36.9% of cases. Other sites of metastasis included bone (47.9%), lung (25.6%), lymph nodes (25.1%), scalp (19.2%), and liver (14.2%). On average, metastases were diagnosed 12.1 months after the most recent resection, and the mean survival from discovery was 5.7 months. In our patients, primary GBM lesions revealed mutations in NF1, TERT, TP53, CDK4, and RB1/PTEN genes. Unique to the metastatic lesions were amplifications in genes such as p53 and PDGFRA/KIT, as well as increased vimentin and Ki-67 expression.

Conclusions: In sum, there is strong evidence that GBMs acquire novel mutations to survive outside the CNS. In some cases, tumor cells likely mutate after seeding scalp tissue during surgery, and in others, they mutate and spread without surgery. Future studies and genetic profiling of primary and metastatic lesions may help uncover the mechanisms of spread.

Keywords: Brain Tumor; Genomic instability; Glioma; Neurosurgery; TP53.