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Letter to the Editor

Letter to the editor regarding "unusual extraneural metastasis of glioblastoma"

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Dear Editor,

We recently read with great interest "Unusual extraneural metastasis of glioblastoma (GBM)" by Achi *et al*., who describe their case of a GBM lung metastasis.[1] We appreciated their commentary on differentiating between GBM and gliosarcoma; however, we believe that their discussion was limited by a superficial overview of the mechanisms by which GBM could metastasize. We wish to provide further elaboration on the various pathways involved in GBM metastasis, with particular emphasis placed on iatrogenic and "glymphatic" mechanisms.

GBM has classically been considered incapable of extracranial metastasis since Cushing and Bailey's famous 1926 report.[7,9,20] However, as described by Achi *et al*., extracranial GBM metastases have been well-reported in the literature.[1] In fact, 0.2–2.7% of GBMs are accompanied by extracranial metastases,[3] and up to 20% of GBM patients have circulating tumor cells present in their bloodstream.[9] The reports describing extracranial GBM metastases in the literature are heterogeneous and reflect the various possible pathways of metastasis. Several metastatic pathways have been described, including leptomeningeal extension,[7,9,21] cerebrospinal fluid (CSF) bulk flow,[15] direct invasion through surrounding tissues, along cranial nerves or spinal nerves,[11,21] hematogenous dissemination,[5] and through the recently described "glymphatic" drainage pathway.[20] We wish to specifically highlight the roles of iatrogenic spread and glymphatic drainage in GBM metastasis.

Iatrogenic tumor spread appears to be the main mechanism by which GBM spreads outside of the head.[3,21] The majority of cases of extracranial GBM metastases described occurred in patients who underwent previous craniotomy, as described in Achi *et al*.'s report;[1,13,25,26] 90–96% of extracranial GBM metastases occurred in patients who underwent prior surgery.[19,25] Surgical intervention inadvertently aids in tumor cell spread by helping tumor cells overcome the obstacles preventing their metastasis, such as the blood–brain barrier (BBB), poor fibronectin expression by tumor cells, and the dense encasement afforded by the dura.[9,18] In addition to surgery, radiation therapy has also been described to promote tumor dissemination by promoting vascular invasion.[9,18,21] Adjunctive procedures commonly performed in GBM patients have also been reported to cause extracranial GBM metastases, including brain biopsy and ventriculoperitoneal shunting.[10]

However, it is important to note that cases of extracranial GBM metastases have been reported independent of any intervention,[2,9,18] and it is possible for tumor cells to overcome the barriers

to their spread unaided.[19] We agree with Sun *et al*., who state that great care should be taken by the operating surgeon to minimize the risk of tumor cell spread.[21] Several actions can be taken to minimize this risk, including adhering to the principles of a nontumor operation, changing gloves and instruments after tumor resection, thoroughly rinsing the surgical field with saline and chemotherapeutics, ensuring an intact dura during closure, and utilizing appropriate adjunctive therapies during the perioperative period.[21,24,25] Most extracranial GBM metastases follow craniotomy, as evidenced by Achi *et al*.'s case, and surgery is the major mechanism responsible for facilitating tumor spread.[1]

The brain does not contain a traditional lymphatic drainage system; however, a recently described "glymphatic" system has revolutionized the understanding of intracranial fluid dynamics.[4,12] Briefly, the periarterial spaces surrounding penetrating arteries and arterioles (Virchow-Robins space) contain CSF, which is subsequently transported across the BBB by aquaporin-4 channels on astrocyte end feet. The transported CSF mixes with the interstitial fluid of the brain parenchyma and is subsequently transported out across the BBB into the perivenous spaces surrounding the deep cerebral veins. These perivenous spaces drain into the dural lymphatics, which ultimately exit the skull and drain into the deep cervical lymph nodes and the systemic circulation.[4,12,19,20] It has been postulated that GBM metastases may occur through this drainage system, as GBM metastases appear to have a predilection for the deep cervical lymph nodes; in fact, 51% of reported extracranial GBM metastases occur in the cervical lymph nodes.[17,26] Furthermore, there have also been several reports of GBM metastases to the parotid gland, which is imbued with a rich lymphatic network during embryological development.[3,14,22,23] Similar to hematogenous dissemination, dural defects created during surgery facilitate tumor cell invasion into the dural lymphatics, and the majority of lymph node metastases occur after prior craniotomy.[2] Nevertheless, we believe the hypothesis that this newly described glymphatic network can independently facilitate that metastasis is valid, as cases of cervical lymph node metastasis have been described independent of surgical intervention.[5,6,8] Current research into the glymphatic system is focused mainly on Alzheimer's disease, stroke, and traumatic brain injury,[12] but we believe that there are important implications for neuro-oncology.

The low reported rate of GBM metastasis is due to the rate of mortality before the development of a recognizable extracranial tumor: [16] The median time between GBM diagnosis and verified GBM metastasis is 2 years,[26] while the medial survival of GBM following initial diagnosis is 13 months.[9] We hypothesize that extracranial GBM metastases may begin to present clinically significant problems as GBM survival increases;[18,20,21,22,25] furthermore, extracranial GBM management protocols do not currently exist.[5,9,21,22,25] Until protocols are developed, we recommend attempting to limit the impact of iatrogenic tumor spread during surgery.[21,24,25] Research into the glymphatic system is ongoing, and we are interested to learn about the potential implications that it may have on neuro-oncology and extracranial metastasis. In conclusion, we commend Achi *et al*.[1] for a fine description of their unusual case of extracranial GBM metastasis, and we hope to supplement their discussion with a brief description of iatrogenic and glymphatic tumor spread.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

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