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Case Report

Extracranial growth of glioblastoma multiforme

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ABSTRACT

We present a 59-year-old woman who noted an enlarging lump on her forehead 6 months after a left frontotemporal craniotomy for tumor resection and chemoradiation of her primary glioblastoma multiforme (GBM). GBM is a highly aggressive intracranial neoplasm associated with the shortest survival time of any primary central nervous system malignancy. Extracranial metastasis is rare, especially without previous surgical disruption of the dura and calvarium, which has been postulated to cause seeding of the extracranial space with tumor cells. This patient's MRI revealed tumor recurrence for which she underwent repeat resection. Histopathology confirmed GBM with unmethylated O-6-methylguanine-DNA methyltransferase and wildtype isocitrate dehydrogenase 1 status, as well as tumor invasion through the bone and subdermal space. The genetic and molecular factors that predict extracranial invasion remain unclear and require further investigation. Emerging data on circulating tumor cells in GBM patients indicate that extraaxial metastasis may be part of the disease course in some, particularly in long term survivors. Furthermore, the proximity of calvarial and scalp lesions to previous surgical sites and the time course in which they emerge after surgery suggests that iatrogenic seeding may also play a role in metastasis. With heightened awareness of the phenomenon, surgical strategies such as watertight approximation of the dura, bone flap replacement, or changing surgical instruments once the intradural component is complete may prove useful to prevent seeding. Prophylactic craniospinal irradiation may also be an appropriate tool in patients at high risk for metastasis, although this population is difficult to identify.

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1. Introduction

Glioblastoma multiforme (GBM) is an aggressive central nervous system (CNS) neoplasm associated with short survival. Extracranial metastasis is rare, with the reported instances attributed to leptomeningeal involvement, cerebrospinal fluid dissemination, direct seeding through craniotomy defects or shunt catheters, and rarely lymphatic or hematogenous spread to distant organs [1]. The rarity of extracranial metastasis has been attributed to the short survival, lack of true lymphatics in the CNS, and physical barriers provided by the dura, extracellular matrix, and basement membrane. We present a patient with GBM infiltration through the calvarium into the dermis.

2. Case report

A 59-year-old woman with recurrent GBM presented with an enlarging forehead lump 6 months after a left frontotemporal

resection, chemoradiation, and bevacizumab treatment. Her MRI revealed tumor invasion through the bone to the subdermal compartment (Fig. 1). The patient underwent tumor resection due to concerns for eventual erosion through the skin with cosmetic and infectious sequelae. Histopathology confirmed GBM with unmethylated O(6)-methylguanine-DNA methyltransferase (MGMT) status and negative isocitrate dehydrogenase 1 (IDH1^{R132H}) staining. Array comparative genomic hybridisation showed a classic signature for GBM including a phosphatase and tensin homolog (PTEN) loss and a single copy gain of the epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor alpha (PDGFRA). Focused sequencing for a panel of oncogenes using OncoMap (version 4; Dana-Farber Cancer Institute, Boston, MA, USA) revealed KRAS and TP53 mutations. Focal spindled reticulin-positive regions were reactive rather than sarcomatous. The patient died 3.5 months after resection. Her case prompts further investigation into the molecular drivers underlying preferential routes of tumor invasion and management strategies to prevent extracranial tumor spread.

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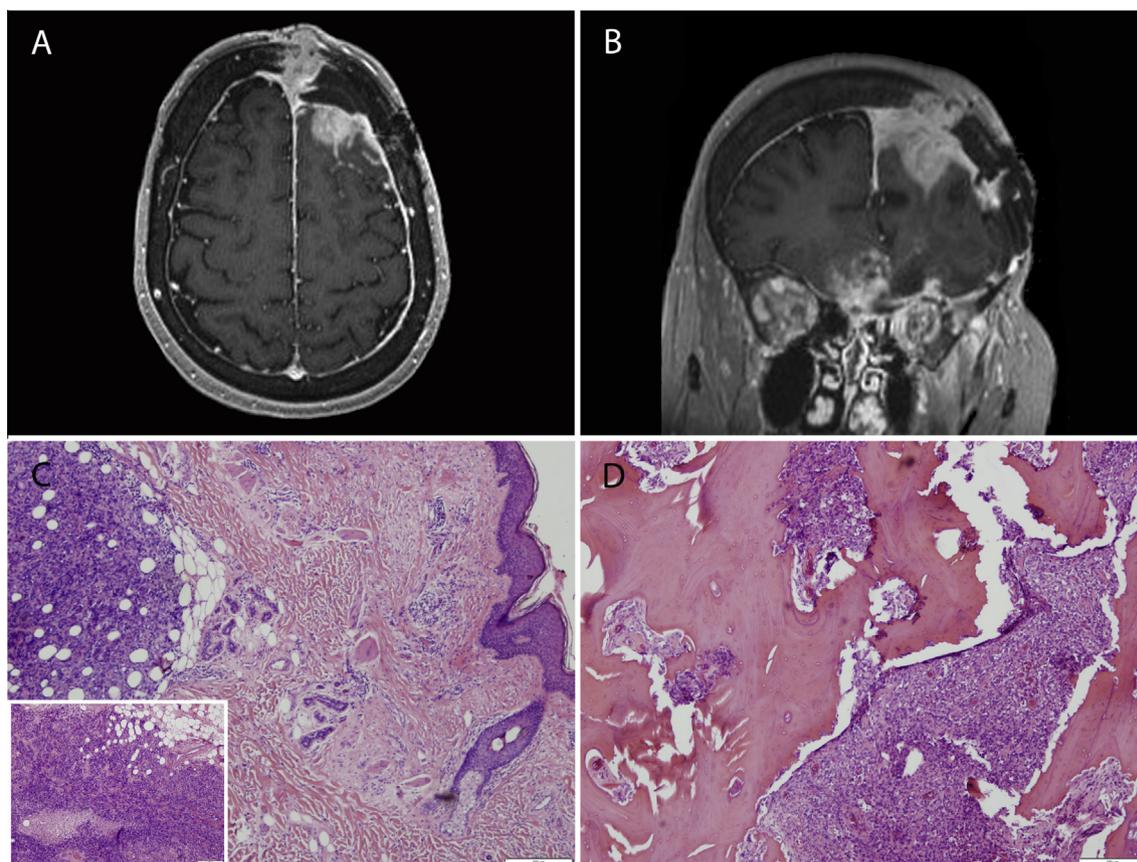


Fig. 1. A gadolinium-enhanced MRI demonstrates (A; axial view) an extra-axial parasagittal tumor extending to and deforming the frontal scalp, as well as (B; coronal view) erosion through the calvarium to the subdermal space. Pathologic examination reveals (C) glioblastoma multiforme invading through the subcutaneous fat and immediately adjacent to hair follicles and other dermal structures (inset: classic pseudopalisading necrosis and vascular proliferation of glioblastoma, intermixed with adipose tissue). (D) Glioblastoma strands intermingled with bony trabeculae and filling the marrow space. (C, D) Hematoxylin and eosin stain; 4 \times magnification; scale bars 100 μ m.

3. Discussion

The current standard of care for GBM combines maximum surgical resection, radiation, and temozolomide chemotherapy. Despite advances in neurosurgical techniques and adjuvant therapies, outcomes remain poor. The rarity of extracranial metastasis translates to the limited understanding of factors influencing spread and how to circumvent it. Potential risk factors include previous surgical resection, long survival and specific molecular markers.

Extracranial GBMs are most often found in patients with prior invasive procedures that iatrogenically generate access to extracranial structures [2]. Approximately 10% of extracranial glioma metastases occur in patients without previous surgery, suggesting that other routes exist [2]. Postulated routes include vascular, lymphatic, perineural, and direct invasion. In our patient, the tumor appears to have spread through a combination of postsurgical seeding through a prior burr hole and direct extension through the bone. Reports of tumor invasion to the skull and overlying scalp tissues are rare [3,4].

Endogenous factors may also predispose patients to extracranial spread of GBM. Circulating tumor cells in peripheral blood are increasingly found across cancers, including in 21% of GBM patients [5]. In comparison, another study noted an only 2.7% incidence of extracranial invasion among 148 GBM patients over 5 years [4]. Thus, it is unclear why extracranial GBM is not observed at an even higher rate than currently reported. One possibility is that a genetic imprint is required, such as EGFR

amplification, that fosters extracranial growth. EGFR amplification has been previously associated with circulating GBM tumor cells and was observed in our patient [5]. Another is the existence of a necessary CNS-specific tumor microenvironment, that predisposes to GBM growth. GBM produce angiogenesis-related factors in their hypoxic and proliferative zones that lead to breakdown of the blood–brain barrier [6]. Transmission of GBM cells, with growth into fatal metastases, has been observed as a complication of organ transplantation [7], suggesting that tumor cells lodge in extracranial organs but may be suppressed by the immune system. Upon transplantation, immunosuppression allows these cells to proliferate in the recipient [7]. A third possibility is that the reported incidence of GBM metastasis is underestimated, as oncologists do not systematically look for metastases outside the brain [8].

Long-term survivors may be at increased risk for extracranial metastases simply as a result of their longer disease course [9]. The rapid disease progression in most patients may not allow time for metastatic evolution, but longer living patients are statistically more vulnerable. While the literature is evolving on this topic, prolonged survival and favorable treatment responses in GBM are associated with multiple genetic factors, including epigenetic silencing of MGMT through methylation [10] and IDH1/2 mutations [11]. Similarly, specific molecular signatures may predict metastatic potential.

Analysis of primary and metastatic lesions in six patients with extracranial invasion, revealed TP53 mutations in four, compared to approximately one third of unselected GBM patients [12].

Notably, different alterations were observed between primary and metastatic lesions in two patients, indicating the emergence of subclones which were distinct from the dominant brain lesion. Further studies with larger sample sizes are needed to elucidate the molecular mechanisms underlying metastatic potential. The identification of such biomarkers may prompt earlier screening for systemic disease in GBM patients.

Emerging data on circulating tumor cells in GBM indicates that extra-axial metastasis may be part of the normal disease course in some. However, the proximity of calvarial and scalp lesions to previous surgical sites and the time course in which they emerge after surgery suggests that iatrogenic seeding may also play a role in metastasis. Heightened awareness can promote surgical strategies to minimize seeding, including watertight dural approximation, calvarial reconstruction, or changing instruments between intradural and extradural segments of the operation [13]. Immediate postoperative prophylactic craniospinal irradiation has also been proposed as a method to prevent extracranial metastases resulting from intraoperative seeding [14]. Increased understanding of the genetic and molecular factors that predict disease course, including extracranial invasion and survival, may further identify therapies for this challenging scenario.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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