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RESEARCH ARTICLE

Postoperative Extracranial Glioblastoma

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ABSTRACT:
Glioblastoma multiforme (GBM) is a WHO grade 4 primary brain tumor with a recalcitrant and dismal prognosis and a 14-month-median survival time. The extracranial spread of GBM is so rare that historically it was not believed to spread outside of the central nervous system (CNS). Since the first extracranial spread of GBM was described in 1928, more cases have been reported. However, the mechanisms have yet to be elucidated due to the rareness of well-documented cases. Here, we reported two cases of GBM with postoperative extracranial spread and reviewed related literature.

Keywords: Glioblastoma, extracranial spread

Abbreviations: CT: Computed Tomography, CNS: Central nervous system, GFAP: Glial fibrillary acidic protein.

Introduction

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults representing 77%-81% of all primary malignant tumors in the central nervous system (CNS)[1], with an incidence of 3.19/100,000 patient-year in the United States (US)[2]. Global investigations have unveiled an annual incidence rate of 0.59 to 5 per 100,000 individuals, with recent research suggesting a rising trend[3, 4]. The mean age of primary GBM is 64 years[2], and the median survival is approximately 14.6 months[1, 5], improving from the previously reported 12 months[6]. It is defined as a grade 4 astrocytoma by the World Health Organization (WHO) classification. The treatment is mainly a surgical resection followed by radiation, chemotherapy, or both. As such a fast-growing and aggressive brain tumor, it is generally and historically believed not to spread to distant organs until Davis reported the first case of disseminated GBM in 1928[7]. Extracranial spread of GBM are extremely rare, affecting 0.4–0.5% of all patients with GBM[8,9] due to the very short lifespan after diagnosis which limits the chance of spread. The mechanism of extracranial GBM is largely unknown although several plausible speculations have been suggested[10-12]. To elucidate the mechanisms of extracranial spread we report two cases of GBM involving the parotid gland and ear canal, along with evaluating and discussing the key factors related to extracranial GBM.

Figure 1

Case presentation

CASE 1

A 54-year-old male presented to the emergency department (ED) with seizures, accompanied by paresthesia in the right upper and lower extremities, and intermittent blurry vision. An MRI revealed a 2.6 cm mildly enhancing left superomedial parietal lobe lesion without significant mass effect (Fig. 1A&B). A biopsy diagnosed glioblastoma (IDH 1/2 wild type, unmethylated). The patient underwent gross total resection followed by combined management with radiation and adjuvant Temodar at an outside institute. After three cycles of Temodar, an MRI showed mixed radiation necrosis and tumor progression. Treatment was ceased, and the patient was transitioned to CCNU + Avastin (Q 42 days) with Avastin (Q 2 weeks). Three months later, he developed a left cheek mass which grew rapidly. A biopsy of the left parotid gland found GBM. Histopathology showed a hypercellular glial neoplasm with nuclear pleomorphism, mitosis, vascular proliferation, and prominent palisading necrosis (Fig. 2A&B), supported by diffuse glial fibrillary acidic protein (GFAP) positivity (Fig. 2C) and pankeratin (AE1/AE3) negativity (Fig. 2D). Radiation with Avastin/Keytruda was restarted, and hospice care began three months later. The patient passed away one month after the initiation of hospice care.

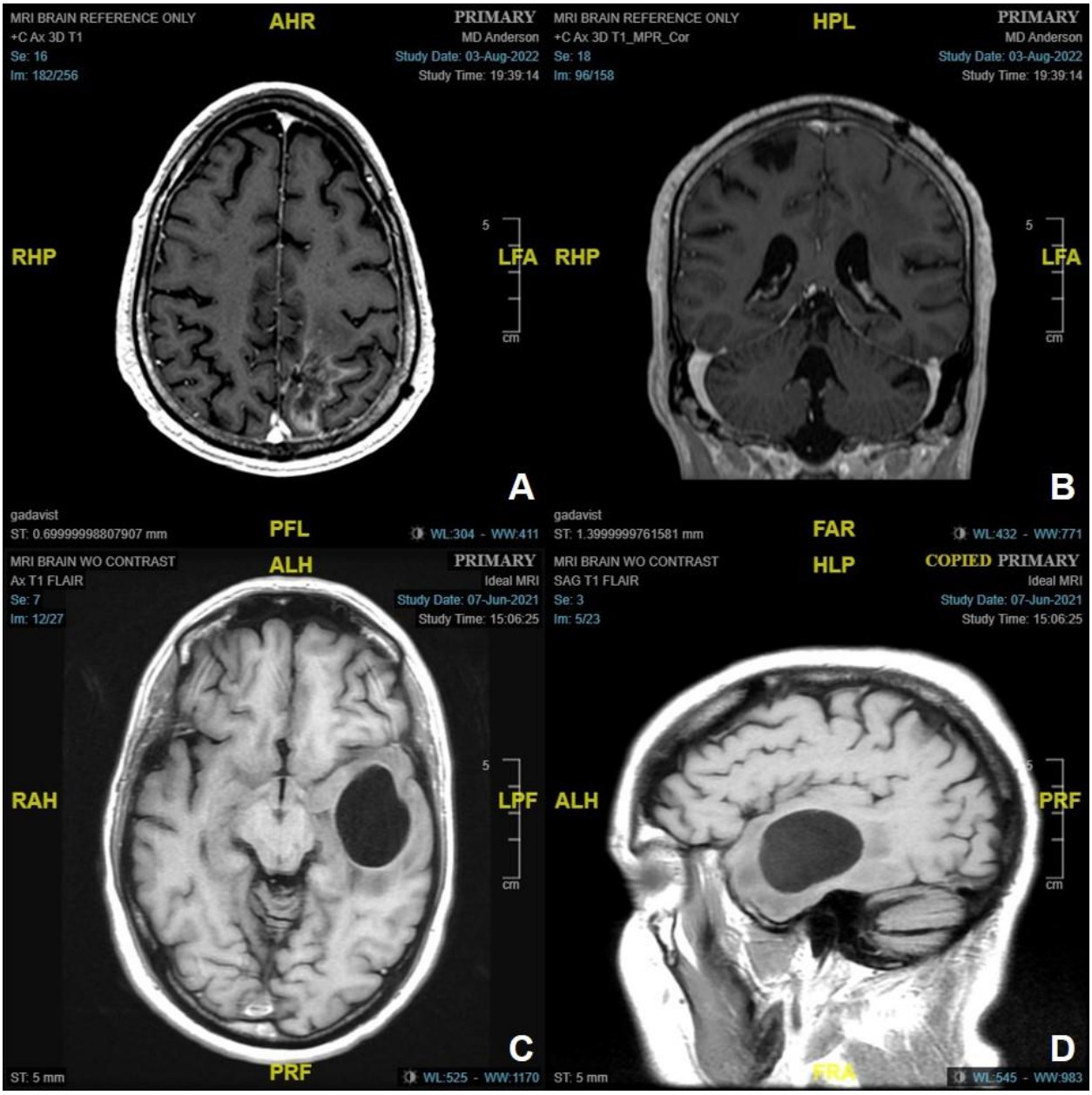

Figure 1. T1 weighted Magnetic resonance imaging (MRI) demonstrates destructive GBM lesions. The first case shows a 2.6 cm left superomedial parietal lesion in Transversal **(A)** and Coronal **(B)** view. The second cases shows a 4.4 cm left temporal cystic lesion in Transversal **(C)** and Sagittal **(D)** view.

Figure 2

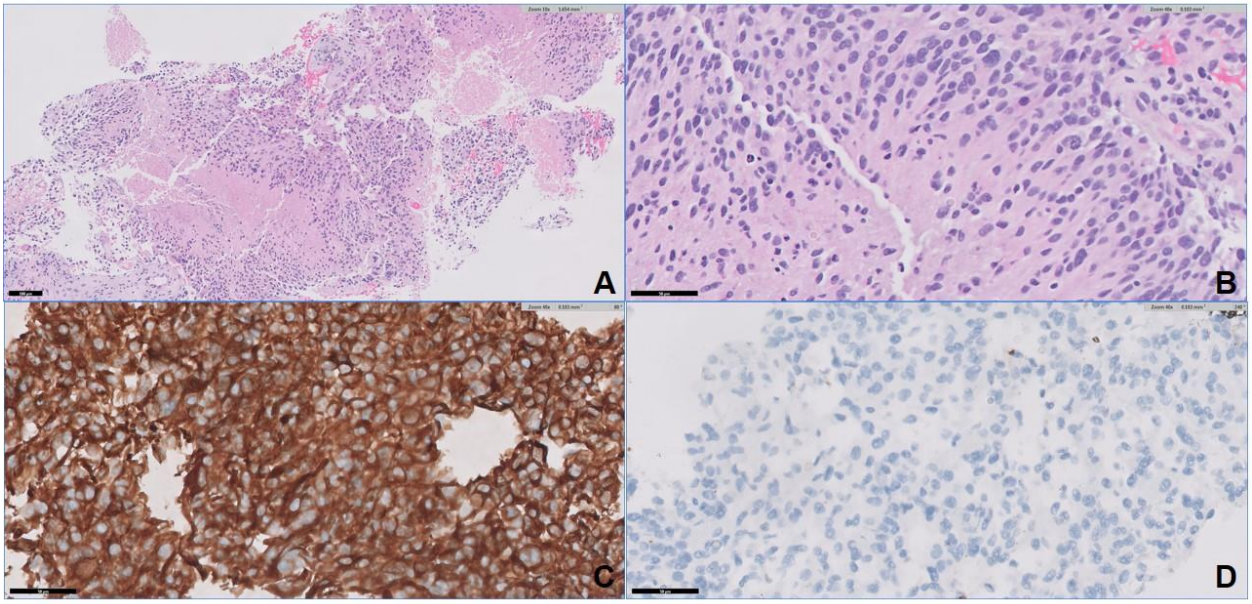

Figure 2. Glioblastoma involving left parotid gland. Hematoxylin and Eosin staining shows hypercellular glial neoplasm with nuclear pleomorphism, mitosis, vascular proliferation and prominent palisading necrosis at 100x magnification **(A)** and 400x magnification **(B)**. The glioblastoma cells are diffusely positive for GFAP **(C)** and negative for pankeratin **(D)**.

CASE 2

A 47-year-old male presented to the ED with a newly discovered brain mass and left-sided headache. He reported nausea, dizziness, speech difficulty, and vision loss in the right eye, but denied limb weakness or numbness. A CT scan showed a 4.4 cm cystic mass in the left temporal lobe (Fig. 1C&D). The initial resection revealed grade 4 glioblastoma (IDH 1/2 wild type, unmethylated). After recurrence, another resection was performed, followed by radiation. An MRI showed a 1.4 cm enhancing mass posterior to the resection cavity, suggesting recurrence. Due to the risks, hospice care was recommended. A CT scan after six months indicated rapid GBM progression, extending from the resection site into the left temporal bone, mastoid sinus, and ear canal. Biopsy of the left ear canal showed skin and subcutaneous tissue with focal malignant cells, ulceration, granulation tissue, and bacterial colonization (Fig. 3A&B), consistent with GBM extension into the ear canal and supported by diffusely positive GFAP (Fig. 3C) and negative pankeratin (AE1/AE3) (Fig. 3D). The patient passed away three months later.

Figure 3

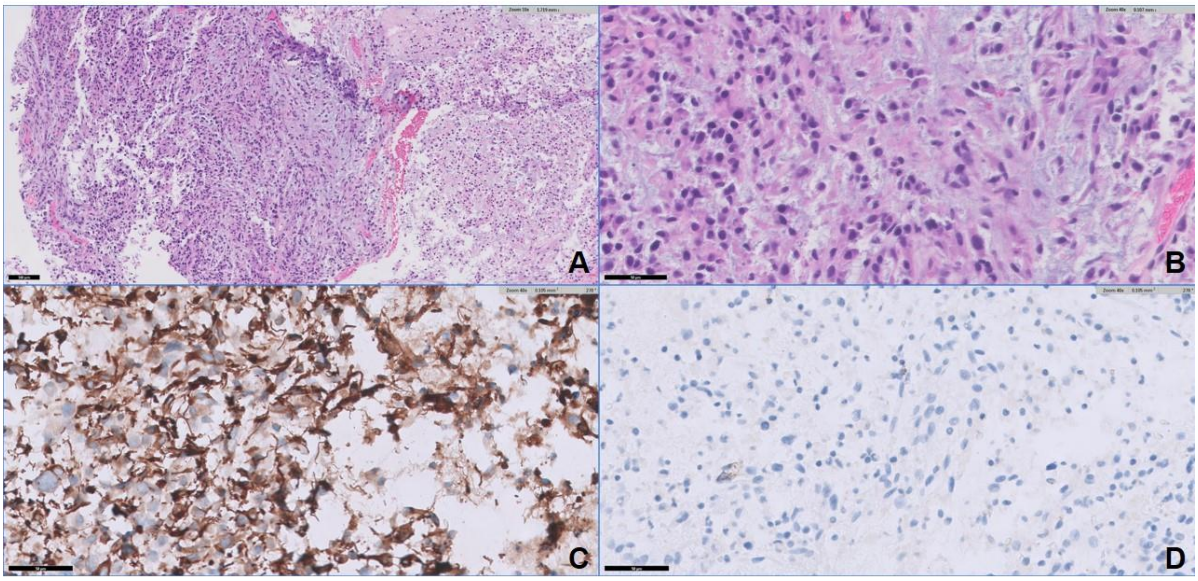

Figure 3. Glioblastoma involving left ear canal. Hematoxylin and Eosin staining shows focal malignant cells with nuclear pleomorphism, vascular proliferation and necrosis at 100x magnification **(A)** and 400x magnification **(B)**. The glioblastoma cells are diffusely positive for GFAP **(C)** and negative for pankeratin **(D)**.

Discussion

Glioblastoma's extracranial spread is exceedingly rare due to strong CNS protective mechanisms, including the lack of a true brain lymphatic system and encased venous sinuses[13]. Due to short survival time, GBM patients often expire before extracranial spread develops, attributed to oncothlipsis, intracranial hypertension, or complications[14]. Historically, GBM was not considered to spread outside of CNS. Despite this, extracranial GBM have been reported with common sites being lungs, lymph nodes, spinal cord, and bone[15]. The mechanism behind extracranial spread of GBM remains uncertain. Factors influencing this phenomenon have been well proposed. Extended patient survival due to improved treatment and early diagnostics[16] increases chances of extracranial spread[10]. Another popular speculation is that the advancement of increasingly assertive neurosurgical treatments damages the protective factors, including the absence of lymphatic vessels, the blood-brain barrier, the dense connective tissue, virtual absence of collagen, and lacking of direct connection between subarachnoid space and hematogenous or lymphatic system[17]. Previous cranial surgery potentially aids tumor cell migration through dura mater, supported by the findings that 96% extracranial GBM cases are status post-surgery[11, 18, 19]. However, recent statistics show around 10% of extracranial GBM occurred without surgical intervention[9], possibly linked to chemoradiotherapy-induced mechanisms[12, 20].

Table 1. Cases of GBM involving parotid gland.

Case	Age	Gender	Location (lobe)	Treatments after surgery	Extracranialsite	Diagnosis to extracranial involvement (months)	Survival post extracranial involvement (months)
1[32]	49	F	Left occipital	Radiochemotherapy	Left parotid gland	5	8
2[22]	58	M	Right temporal	Radiochemotherapy	Right parotid gland	15	1
3[21]	33	M	Left frontal	Radiochemotherapy	Left parotid gland	6	3
4[17]	26	M	Frontal	Radiochemotherapy	Left parotid gland	7	17
5[33]	53	M	Left temporoparietal	Radiochemotherapy	Left parotid gland	6	4

Case	Age	Gender	Location (lobe)	Treatments after surgery	Extracranialsite	Diagnosis to extracranial involvement (months)	Survival post extracranial involvement (months)
6[34]	56	F	Right temporal	Radiochemotherapy	Right parotid gland	5.5	9
7[35]	52	M	Left temporal	Radiochemotherapy	Left parotid gland	3	3
8[35]	41	M	Left temporal	Radiochemotherapy	Left parotid gland	15	2
Our case 1	54	M	left superomedial parietal	Radiochemotherapy	left parotid gland	10	5

Our study encompasses two male GBM patients, aged 54 and 47 years, both presenting extracranial spread. The first patient exhibited a spread to the left parotid gland, a location which about 8 cases were reported[21-24] (table 1, including our case). Across these cases, the average diagnosis age is around 47 years, marking a 17-year younger than the mean age of primary GBM presentation reported by Thakkar JP *et al*[2]. The mean survival period is 13.8 months, nearly one month shorter than the average14.6 months. Among these cases, four are specifically associated with the temporal lobe, accounting for roughly 44.4% of the total instances. The remaining five cases within the compilation, including our own, originate from diverse primary locations, such as the parietal, frontal, and occipital regions. Additionally, there are seven male and two female patients. Our second patient had a direct extension to the left ear canal. A noteworthy commonality in our two cases lies in their neuroanatomic location, which could be linked to distinct mechanisms of extracranial spread. It's plausible that the spread along the neuraxis[25] could explain both of our cases, as the eighth cranial nerve passes through the ears and the seventh cranial nerve traverses the parotid glands, respectively. Our left ear canal spreading case could also be explained by a direct invasion, where the primary GBM lesion is in the left temporal lobe, close to the left temporal bone. It's worth considering local invasion through the temporal bone[26] as an explanation of the extension into the left ear canal. Remarkably, cases of brain tumors exhibiting direct extracranial extension are not as frequently reported as those involving distant spread. This makes our case of extension into the left ear canal the first of its kind. In addition to GBM, several other high-grade primary brain tumors have the potential to extend beyond the cranial cavity. For instance, high-grade meningiomas, while most typically benign, can exhibit cerebrospinal fluid (CSF) dissemination, resulting in tumor growth beyond the confines of the brain. Similarly, aggressive tumors such as medulloblastoma and primitive neuroectodermal tumor (PNET) share this characteristic of CSF dissemination, making their clinical management particularly challenging[27]. As a result, continuous and comprehensive neuroimaging studies, covering both the brain and spinal cord, are imperative for long-term monitoring.

Nearly two decades ago, a novel chemotherapy approach known as the "Gliadel wafer" emerged and was adopted by surgeons and oncologists[28]. This innovative form of chemotherapy involved the incorporation of carmustine, a chemotherapy agent, into a wafer-like material, which was then surgically implanted into the resected tumor bed following the debulking of the primary tumor mass, typically GBM. The purpose of this implantation was to facilitate localized chemotherapy, targeting any residual tumor cells. However, this pioneering procedure eventually fell out of favor for several reasons[29]. One primary concern was that surgeons observed potential delays in wound healing, possibly attributed to the inhibition of new tissue growth by the chemotherapy agent. Moreover, in some cases, tumor cells appeared to migrate through the surgical wound and congregate, forming localized nodules in the head and neck region. Biopsies of these nodules revealed the presence of GBM cells, suggesting that these cells, while initially sensitive to the local chemotherapy agent, had the capability to migrate to distant areas and form new growths. This phenomenon can largely be attributed to the infiltrative and migrating nature of astrocytes cells. Notably, a few case reports have documented these findings, serving as additional evidence of extracranial tumor extension[27]. It appears that the "Gliadel wafer" treatment is one potential explanation for the extracranial extension of glioma, but it does not apply to our ear canal extension case.

High-grade gliomas such as GBM can be difficult to differentiate from other tumors on the basis of light microscopy alone due to the presence of necrosis,

small sample size, stereotactic biopsies, as well as not familiar to most common pathologists. GFAP, isolated from aging multiple sclerosis plaques by Roy and Sarkar, serves as a key marker in neuro-oncology diagnosis, demonstrating positive reactions in astrocytomas, ependymomas, mixed gliomas, subependymal giant cell astrocytomas, pleomorphic xanthoastrocytomas, astroblastomas, and gliosarcomas[30]. In both our two cases, GFAP staining shows strong diffuse positivity. However, GFAP negative metastatic GBM has been reported[31]. In this case, a careful interpretation of histological, immunohistochemical, and clinical data is warranted.

Effective treatment for extracranial GBM remains elusive, yielding poor prognosis[12]. For high-grade and low-grade gliomas, maximal surgical resection followed by prompt radiotherapy and chemotherapy can delay recurrence and extend survival. Surgeons must prevent implantation and minimize tissue damage since residual tumor impairs radiotherapy and chemotherapy efficacy. Swift and precise treatment, initiated promptly upon the discovery of extracranial GBM, is essential for preventing further progression. Therefore, it is crucial to assess potential extracranial involvement by employing periodical CT scans with pathology confirmation if needed. It is also important for clinicians understanding the possibility of extracranial spread of high-grade brain tumors, in order to facilitate the diagnosis and treatment.

Conclusions

GBM stands as the most prevalent primary malignant CNS tumor, with a poor prognosis and rarely extracranial spread. However, there has been a discernible upward trajectory in the incidence of extracranial spread as evidenced by reported cases spanning the previous century. Despite various proposed theories, the intricate mechanics of glioma spread remain unclear, owing to its scarcity and dire prognosis, impeding in-depth investigation. The rising incidence of extracranial spread underscores the need for more in-depth investigation into their underlying causes.

Abbreviations: CT: Computed Tomography, CNS: Central nervous system, GFAP: Glial fibrillary acidic protein

Conflicts of Interest Statement: The authors have no conflicts of interest to declare.

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