Infratentorial Glioblastoma Metastasis to Bone

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Key words
- Glioblastoma multiforme
- Isocitrate dehydrogenase (IDH1/IDH2)
- Metastasis
- Spine

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
GBM: Glioblastoma
GFAP: Glial fibrillary acidic protein
IDH: Isocitrate dehydrogenase
MRI: Magnetic resonance imaging
PNC: Primitive neuronal component
PNET: Primary neuroectodermal tumor
WHO: World Health Organization

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BACKGROUND: **Glioblastoma multiforme (GBM) is a rapid-growing central nervous system neoplasm. We report a case of GBM with extensive intramedullary lumbar drop metastasis and highly unusual osseous spine metastasis from a primary infratentorial GBM occurring 10 years after the initial diagnosis, which to our knowledge has not been described previously.**

CASE DESCRIPTION: **This 37-year-old man presented with new-onset headaches of increasing severity. Brain magnetic resonance imaging (MRI) demonstrated a heterogeneously enhancing mass in the left superior temporal lobe with adjacent edema. The lesion was initially biopsied in December 2006 and diagnosed as GBM (World Health Organization grade IV) with characteristic features of a highly cellular infiltrating glial neoplasm with nuclear pleomorphism, abundant microvascular proliferation, and abundant necrosis with pseudopalisading nuclei. Ki-67 immunostaining revealed that 15%–20% tumor cell nuclei were positive, indicating a high proliferative index. Histologically, this neoplasm demonstrated characteristic "cell wrapping." Immunoreactivity was variably but strongly positive for glial fibrillary acidic protein in neoplastic cells. In 2018, additional MRI revealed disease throughout the spine and bone biopsy of the thoracic spine showed the same glial neoplasm with primitive neuroectodermal tumor–like components (GBM-PNET).**

CONCLUSIONS: **This case is meant to highlight that, although rare, infratentorial GBM-PNET has a higher frequency of isocitrate dehydrogenase 1 (*IDH1*) mutation and may metastasize to the spine years after the initial diagnosis despite the likely better prognosis.**

Glioblastoma multiforme (GBM) is a rapid-growing, central nervous system neoplasm typically treated by surgery, followed by chemotherapy and radiation therapy.[1] With the current standard of care treatment, median survival time is limited to 12–15 months.[2,3] Whereas GBM has a propensity for local invasion, only approximately 2% of cases exhibit dissemination outside of the central nervous system.[4] GBM with a primitive neuronal component (GBM-PNC) is a rare variant of GBM that often arises from a preexisting high-grade glioma and has a high propensity for cerebrospinal fluid (CSF) dissemination. GBM has been reported to have a median survival time of 10 months after initial metastasis to the spine; metastasis to the spine is documented in 0.4%–0.5% of cases.[5-7]

CASE PRESENTATION

History

A 37-year-old right-handed man was diagnosed with GBM involving the left temporal lobe in 2006 after presenting with progressively worsening new-onset headaches.

Examination

Pathological evaluation confirmed a World Health Organization (WHO) grade IV GBM, for which the patient underwent surgery.

Operation

In 2006, the patient initially underwent a craniotomy for left temporal lobe tumor resection, followed by chemoradiotherapy. The patient was subsequently monitored with surveillance magnetic resonance imaging (MRI), as shown in Figure 1, and underwent 4 more resections in October 2008 (left temporal lobe), January 2016 (cerebellum), February 2017 (left temporal lobe), and July 2017 (left temporal lobe). Each resection was found to be consistent with GBM on pathology (see below).

Within the foregoing time period, the patient also underwent multiple rounds of radiochemotherapy. In 2006, the patient received temozolomide, intra-arterial carboplatin and localized gamma knife boost (15 Gy). The patient did not receive adjuvant therapy with the 2008 resection, because pathology was negative for malignancy. Between January 2010 and July 2011, he received temozolomide for a new area of nodular enhancement along

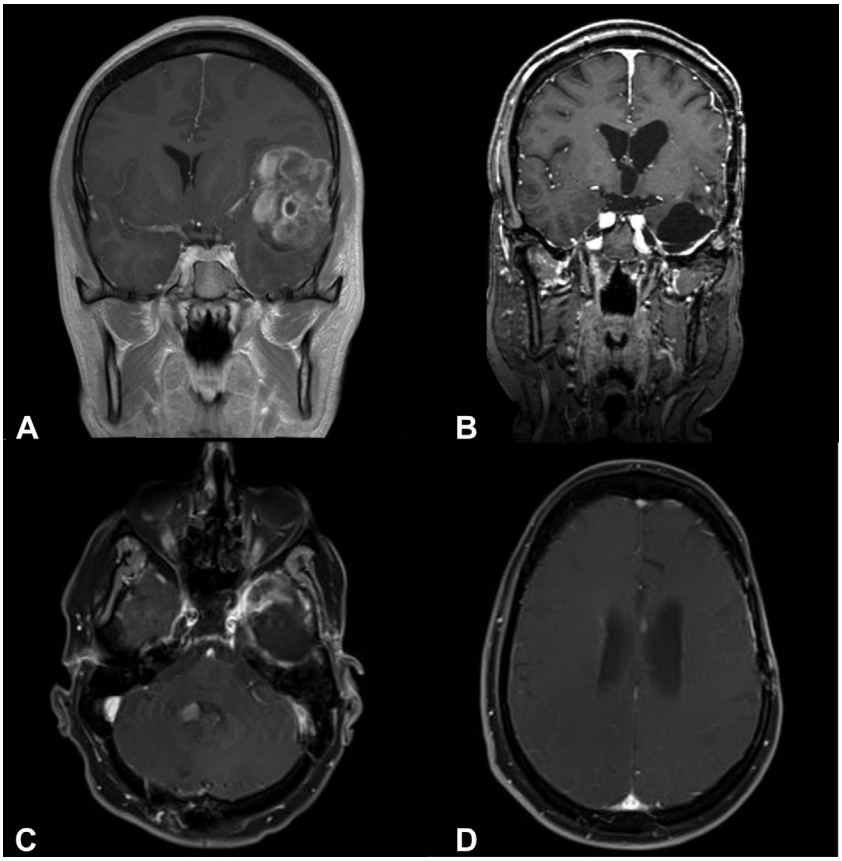

Figure 1. Magnetic resonance imaging (MRI) findings. (**A**) In 2006, coronal T1-weighted MRI showing a 5-cm heterogeneous mass in the left superior temporal lobe with adjacent edema. (**B**) In 2018, reconstruction coronal T1-weighted MRI with contrast showing postsurgical changes in the left temporal lobe, with no new enhancement with resection cavities. (**C**) In 2018, MRI showing a new enhancing subependymal lesion at the right aspect of the fourth ventricle measuring 1.1 × 0.8 × 1.3 cm. (**D**) A new enhancing focus on the seventh ependymal surface of the corpus callosum at the septum pellucidum measuring 0.8 × 0.4 × 0.5 cm. In (**C**) and (**D**), the new enhancing lesions represent metastatic foci.

the floor of the left temporal lobe resection cavity. Surveillance MRI was stable until January 2016, when it revealed a new enhancing mass in the right cerebellum. Between March 2016 and April 2016, the patient received radiation therapy (60 Gy total in 30 fractions) to the right cerebellum and temozolomide.

In January 2017, MRI revealed a new enhancing lesion in the surgical cavity of the left temporal lobe. Resection was performed, and GBM was identified on pathology. The patient completed 4 cycles of immunotherapy (pembrolizumab) and started treatment with the Optune device (Novocure, Jersey, UK). These treatments were discontinued when MRI in June 2017 revealed a recurrent enhancing lesion in the left temporal lobe resection cavity. Resection was performed, and GBM was identified on pathology. Postoperative MRI revealed complete resection, but a small right cerebellar lesion was noted concerning for disease. Given the patient's recent craniotomy, he underwent gamma knife stereotactic radiosurgery (24 Gy) to the new cerebellar lesion as well as to the left temporal resection bed (22 Gy) in August 2017. He was then restarted on treatment with the Optune device and pembrolizumab. Surveillance MRI in October 2017 was suspicious for recurrent disease in the left temporal lobe, as well as new leptomeningeal involvement. Avastin was added to treatment plan. Repeat MRI in December 2017 showed continued changes in the lateral ventricles and leptomeningeal involvement, for which he received reirradiation (37.5 Gy in 15 fractions) of the left temporal resection cavity and bilateral lateral ventricles in January 2018.

Imaging in March 2018 showed a positive treatment response, with near-complete resolution of contrast enhancing disease. Two months later in May 2018, the patient developed left leg pain and mid-thoracic back pain. MRI revealed disease throughout the spine, and bone biopsy of the thoracic spine showed a primary neuroectodermal tumor (PNET). A course of palliative radiation therapy (8 Gy) was given to the T6—T8 vertebral bodies. The patient was later discharged to hospice after imaging showed a paraspinal hematoma, significant progression of disease in left temporal lobe resection cavity, and increased size of the ependymal and leptomeningeal metastatic lesions. The patient subsequently died in July 2018.

Pathological Findings

The patient's first tumor was diagnosed in December 2006 as a WHO grade 4 GBM with characteristic features of a highly cellular neoplasm, nuclear pleomorphism, abundant microvascular proliferation, and abundant necrosis with pseudopalisading nuclei. Ki-67 immunostaining revealed 15%—20% positive tumor cell nuclei, indicating high mitotic activity. In October 2008, after resection for the ring-enhancing mass, MRI demonstrated gliosis of the left temporal lobe without definitive disease recurrence.

Recurrent GBM was demonstrated histologically in January 2016 with the right cerebellar lesion. Features included moderate cytologic atypia and pleomorphism with moderate mitotic activity and apoptosis. Microvascular proliferation was seen focally, but with no evidence of necrosis. Recurrent GBM was demonstrated histologically in February 2017 with the left temporal lesion. Features included a densely cellular astrocytic neoplasm with marked nuclear pleomorphism and frequent mitoses. There were rare foci of vascular proliferation, with no necrosis

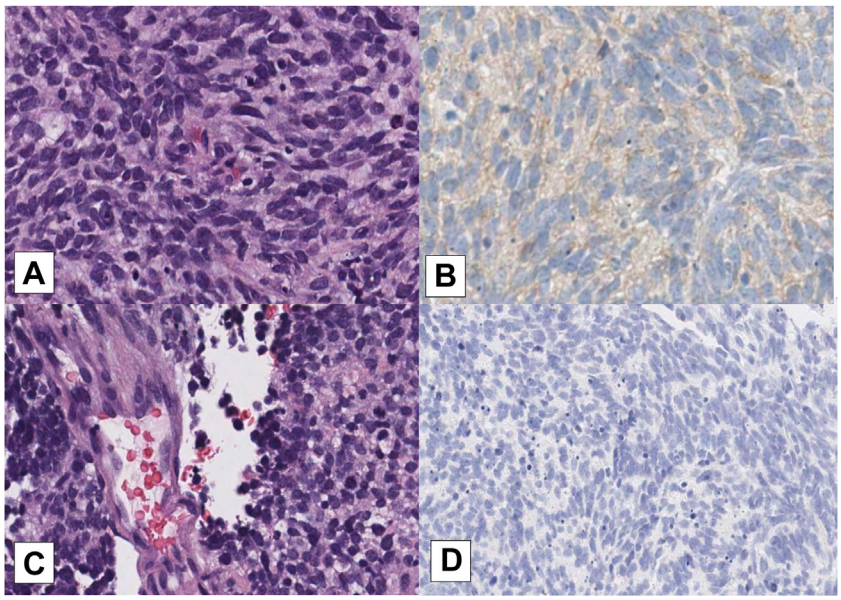

Figure 2. Recurrent glioblastoma multiforme. (**A**) Highly cellular astrocytic neoplasm with nuclear pleomorphism. (**B**) Diffuse synaptophysin reactivity within neoplastic cells. (**C**) Microvascular proliferation with an adjacent mitotic figure. (**D**) IDH1 (R132H)-negative.

seen. Recurrent GBM was demonstrated histologically in July 2017 with the left temporal lobe resection cavity lesion. Features were very similar to those seen at the previous resection. Neoplastic cells showed patchy weak to moderate intensity immunoreactivity for synaptophysin, as shown in Figure 2, and were negative for isocitrate dehydrogenase 1, (IDH1; R132H). Spinal bone biopsies from the cervical and thoracic regions revealed a GBM-PNC (2016 WHO classification), previously termed GBM with PNET-like components. Histology revealed a primitive-appearing neoplasm with carrot-shaped to somewhat spindle-appearing cells with increased mitotic activity, apoptosis, "cell wrapping," and immunoreactivity for synaptophysin, as shown in Figure 3. Immunoreactivity was variably positive for glial fibrillary acidic protein (GFAP) in neoplastic cells.

Postoperative Course

Following chemotherapy, whole-brain radiation, and radiosurgery, the patient developed simple partial seizures in 2007, confirmed via electroencephalogram monitoring, and was started on antiepileptic therapy. In 2010, a new region of nodular enhancement in the left temporal lobe was treated with Temodar for a total of 15 cycles. The treatment was discontinued early because of side effects. After discontinuation of Temodar, the patient experienced a small infarction in the brainstem, causing left-sided weakness in the arms and legs that required extensive rehabilitation, a treatment effect due to the discontinuation of Temodar.

DISCUSSION

GBM is an aggressive malignant brain tumor. Despite advances in surgical resection and adjuvant chemoradiotherapy, the prognosis for patients with GBM remains poor, with a median survival of 12–15 months.[2] The estimated 3-year survival is just 10.3%.[8] IDH-mutant GBMs have significant survival benefits and a more favorable prognosis compared with IDH wild-type GBMs.[9-13] Patients with long-term survival are often younger, with *IDH1*/*IDH2* mutant and MGMT-methylated tumors.[14-18]

Malignant gliomas represent approximately 60% of all primary brain tumors in adults; however, metastases occur in <2% of cases, some of which include astrocytoma, oligodendroglioma, and GBM. It is estimated that only 1.1% of patients have spinal metastasis at 5, 8, and 11 months after craniotomy,[7] with a median interval between diagnosis of intracranial disease to diagnosis of metastases of 14.1 months.[19] The median duration of survival from initial GBM metastasis to the spine is just 10 months.[6]

GBM-PNC was added as a subclassification of GBM to the WHO 2016 classification of tumors of the central nervous system.[20] This subclassification was previously referred to in the literature as GBM with a PNET-like component. GBM-PNC frequently arises within a preexisting malignant glioma, most often an *IDH1*/*IDH2* mutant GBM. Metastasis of GBM to the spine is a rare manifestation[1,4,6,11,21]; however, GBM-PNC tumors have a tendency for CSF dissemination.[22]

It is important to note the ways in which our present case differs from previously reported cases. Extraneural metastasis from primary central nervous system neoplasms typically occurs after a median interval of 2 years from diagnosis.[4,23] In our case, the patient was diagnosed with GBM metastasis to the spine at 11 years after the initial diagnosis. Our patient's spinal metastasis was identified as GBM-PNC, a rare variant of GBM with a relatively higher propensity for CSF dissemination. On histology, the tumor was found to have features consistent with GBM-PNC, including carrot-shaped nuclei, cell-to-cell wrapping, and diffuse synaptophysin, but with variable GFAP immunoreactivity. Extensive intramedullary lumbar drop metastasis was identified, a rare complication that occurs in 1% of patients with GBM.[24]

Osseous metastasis to the spine from infratentorial GBM is very infrequent, as previous reports have largely included only patients who had primary supratentorial tumors.[21,25]

The IDH status of the patient's GBM was not defined. Immunohistochemistry showed that the GBM had normal IDH1 (R132H). Molecular testing demonstrated a *PIK3CA* mutation and a pathogenic *TP53* mutation. No *IDH1*/*IDH2* mutations were identified in this case. In our patient, the GBM metastasized from an infratentorial GBM to the spine by 11 years after initial diagnosis. This case report highlights that GBM may metastasize to the spine years

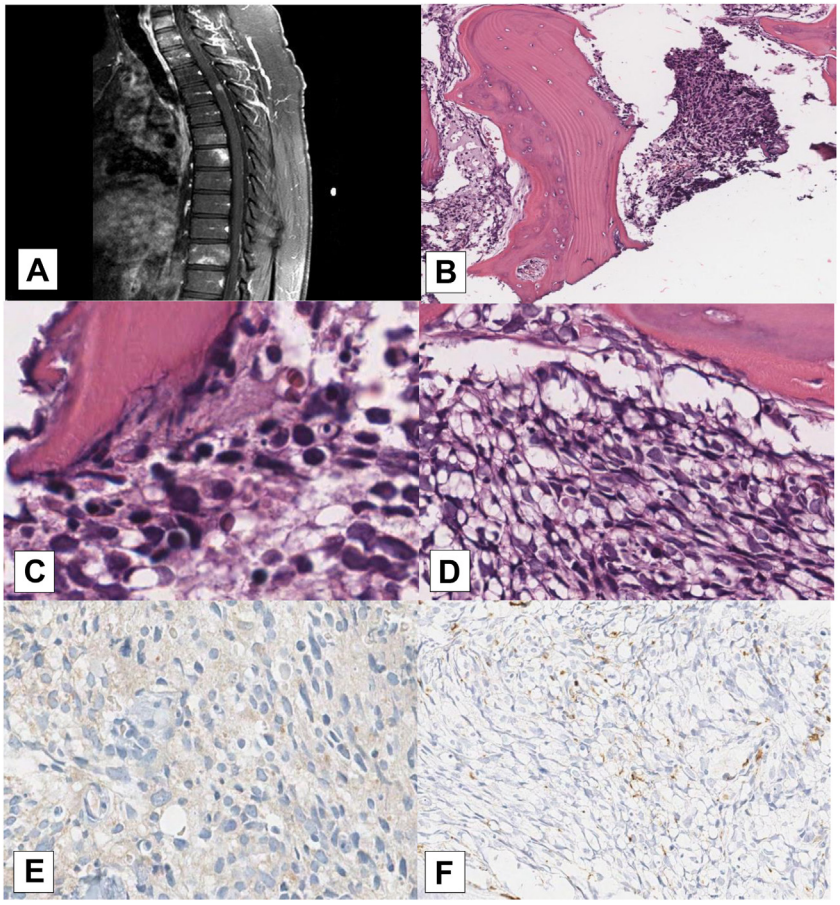

Figure 3. Glioblastoma with a primitive neuronal component spinal osseous metastasis (**A**) Sagittal magnetic resonance imaging of spine. (**B**) Basophilic tumor (right) adjacent to eosinophilic decalcified bone (left). Original magnification 10×. (**C** and **D**) Tumor showing features of nuclear pleomorphism, high cellularity, nuclear molding, and cell-to-cell wrapping. Original magnification 40×. (**E**) Extensive synaptophysin reactivity. (**F**) Glial fibrillary acidic protein variably positive.

after the initial diagnosis. The causes of death for patients with GBM are varied and multifactorial, which could explain why our patient was still alive more than a decade later; however, in general, death is often due to tumor progression.[26,27] GBM-PNCs have been found to arise from pre-existing high-grade gliomas, and this is likely what occurred in our patient.

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