Spinal Metastases of Supratentorial Glioblastoma with Primitive Neuronal Component

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Key words
- Component
- Glioblastoma
- Metastases
- Neuronal
- Primitive
- Spinal

Abbreviations and Acronyms
- CNS: Central nervous system
- GBM: Glioblastoma multiforme
- MRI: Magnetic resonance imaging

INTRODUCTION
Glioblastoma multiforme (GBM), the most common primary brain tumor, accounts for >50% of malignant primary brain tumors.¹ Standard therapy consists of the Stupp protocol of surgical resection followed by concomitant radiation and chemotherapy and adjuvant chemotherapy.² Although overall survival averages 14 months,³ only 40% of patients survive the first year, and only 5% survive >5 years.³ Nearly all patients with GBM experience relapse, and relapse is usually local.⁴ The rare relapses that develop outside of the brain are typically found in the spinal cord associated with cerebrospinal fluid dissemination.⁵ Dissemination can occur at any time point in the disease course and is observed most often in young patients.⁵,⁶ In particular, GBMs with primitive neuronal components exhibit dissemination rates up to 40%⁷ and often arise from a lower grade precursor.

We report a patient who had a supratentorial GBM with a primitive neuronal component who developed spinal metastasis during the disease course. Our case highlights the following topics that are discussed in the literature: 1) immunohistochemical patterns differ between the primary tumor and spinal metastasis (the latter with no glial and only minor neuronal differentiation); 2) spinal dissemination typically shows leptomeningeal or ventricular invasion by the primary tumor; and 3) patients’ overall short survival times with GBM are likely insufficient for metastases to grow enough to become symptomatic, and thus rates of dissemination may be underestimated.

CASE DESCRIPTION
History and Examination
A 47-year-old man initially presented with personality changes characterized by lack of attention, slowing down, and mild cognitive impairment. His past medical history included acute leukemia during childhood; however, details on the diagnosis and treatment were not available. At presentation, neurologic examination showed a slight left-sided hemiparesis, and magnetic resonance imaging (MRI) of the brain revealed a large cystic tumor in the right temporal lobe (Figure 1).

Treatment
The patient underwent a temporal lobe resection that achieved total resection of the solid tumor and subtotal resection of the cystic components. Based on the histopathologic findings of a GBM, the current standard of care was initiated, as follows. Concomitant radiotherapy (total dose 60 Gy) was combined with continuous daily temozolomide (75 mg/m²) followed by additional adjuvant temozolomide (200 mg/m² for 5 days during each 28-day cycle). Initially, the patient did well on this protocol with no relevant treatment-associated toxicities. His cognitive symptoms improved, and he was able to work part-time.

After completion of 3 treatment cycles, follow-up brain MRI showed new contrast-enhancing areas in the temporal white matter and corpus callosum. These MRI findings were interpreted as pseudoprogression, and adjuvant treatment with temozolomide was continued. The patient presented 1 week later with right-sided shoulder and neck pain that was treated with analgesics. Several weeks later, he developed a slight right-sided...
hemiparesis. Another brain MRI performed at that time revealed regression of the contrast-enhancing areas in the temporal white matter and corpus callosum. The patient’s symptoms subsequently persisted and worsened to include progressive numbness of the right arm, intermittent numbness of the left arm, and increasing paresis of the lower limbs with exacerbating shoulder pain. MRI of the cervical spine showed 3 intramedullary and extramedullary hyperintense and contrast-enhancing lesions, one of which led to absolute stenosis of the spinal canal (Figure 2). Owing to the patient’s clinically deteriorating paresis, surgical decompression and biopsy were performed.

**Histopathology**

Histopathologic examination of the temporal lobe tumor showed an astrocytic pleomorphic component with microvascular proliferation and necrosis as well as primitive nodules with high cellularity and a high nuclear-to-cytoplasmic ratio. These areas did not express glial fibrillary acidic protein and showed partial immunopositivity for CD56, CD99, NeuN, synaptophysin, and vimentin (Figure 3). Histopathologic examination of the spinal metastasis revealed an epithelioid neoplasia with high cellularity and high nuclear-to-cytoplasmic ratio. Immunohistochemistry detected expression of CD99, CD56, ATRX, and NeuN with negativity for synaptophysin, S100, glial fibrillary acidic protein, and cytokeratin. Ki-67 labeling index was 50% (Figure 4 and Table 1).

**Postoperative Course**

After resection of the spinal lesion that was responsible for the spinal canal stenosis, the patient developed lower extremity–dominant tetraparesis. After discussing the biopsy findings at our multidisciplinary tumor board, a course of radiotherapy was started. Subsequently, with lack of any major clinical improvement and the patient’s poor condition, these systemic therapies were discontinued, and the patient died of his disease.

**DISCUSSION**

We present a case of a supratentorial GBM with a primitive neuronal component in an adult patient with spinal metastasis during the disease course. Leptomeningeal spread of GBM is a rare but known entity in the literature usually occurring late in the disease course. Incidence rates of 2%–4% are reported, with higher rates in the case of cerebellar GBM. Cerebrospinal fluid dissemination of malignant gliomas with primitive neuronal components have been previously described in a case series by Perry et al. In that study, 53 patients (median age 54 years) with GBM with primitive neuronal components were examined, and 8 (15%) developed cerebrospinal fluid metastases. In an autopsy series of 8 patients with a GBM diagnosis by Willard and Kleinschmidt-DeMasters, 4 patients showed metastases, 1 with a primitive neuronal component.

**Tumor Dissemination Trends, Locations, and Immunohistology**

In contrast, autopsy series have reported dissemination rates up to 25%. As
mentioned, Willard and Kleinschmidt-DeMasters\textsuperscript{18} identified 4 metastases in 8 cases of GBM, including 1 with a primitive neuronal component. In an early autopsy series in the 1970s, Erlich and Davis found that 5 of 20 spinal cords of patients with GBMs had spinal metastases.\textsuperscript{9} Therefore, we believe that dissemination is likely more common than thought but rarely looked for because of poor prognosis of the leading primary tumor. Additionally, the idea that most patients do not develop symptoms from their metastatic lesions was postulated by Vertosick and Selker,\textsuperscript{19} who observed that dissemination became symptomatic in only 2\% of their cases. In their series of GBMs, this low rate of symptomatic dissemination was explained by the patients' overall short survival times, which were most likely insufficient for the metastases to grow enough to become symptomatic. As survival times of patients with dissemination were not significantly lower than their general GBM population, Vertosick and Selker\textsuperscript{19} postulated that they have better prognostic features, allowing the metastastic tumors to grow to a symptomatic size. However, from the onset of metastases, the survival time was short with a median of 2.8 months. Therefore, these authors hypothesized that patients presenting with symptomatic metastases could have a better prognosis in general, which could explain their not much inferior survival compared with patients without dissemination.

Younger age and tumor location are among several risk factors for tumor dissemination.\textsuperscript{5,19} In their autopsy series, Erlich and Davis\textsuperscript{9} reported that patients averaged 34 years with spinal seeding compared with 58 years without seeding. Their findings were similar to the series reported by Arita et al.,\textsuperscript{5} in which patients averaged 31 years with dissemination versus 44 years without dissemination.

Autopsy findings by Bryan\textsuperscript{5} that all cases with intraventricular seeding had primary tumor invasion of the ventricles were similar to findings reported by Erlich and Davis,\textsuperscript{9} in which all cases with spinal dissemination showed leptomeningeal or ventricular invasion by the primary tumor, and the findings in our case, with spinal metastases that disseminated from a periventricular tumor. In general, GBMs in infratentorial locations seemed to have higher seeding rates than tumors in supratentorial locations (60\% vs. 30\%) in an autopsy series by Salazar and Rubin.\textsuperscript{8} Although Tsung et al.\textsuperscript{17} found only 4 (19\%) of 21 patients with cerebellar GBM in their

![Figure 2. (A–E) Magnetic resonance imaging depicting dissemination effect as intramedullary spinal cord solid metastasis. Precontrast sagittal and axial T2-weighted (A and D), sagittal T1-weighted (B), and sagittal and axial T1-weighted fat-saturated postcontrast (gadolinium) (C and E) images. Note metastasis associated with spinal cord edema and mass effect at cervical (white arrows) and thoracic (open arrows) levels and at termination of dural sac (thin white arrow in C).]
Figure 3. Histologic studies confirm glioblastoma multiforme with a primitive neuronal component. (A) Diffuse astrocytic component (right) and primitive neuronal component (left) (original magnification, ×200). (B) Microvascular proliferation and many mitoses on hematoxylin and eosin staining (original magnification, ×400). (C) Reduction of glial fibrillary acidic protein immunoreactivity in the neuronal component (original magnification, ×400). (D) Expression of CD56 in the neuronal component (original magnification, ×400).

Figure 4. Histologic features of the spinal metastasis. (A) Epithelioid-like neoplasia on hematoxylin and eosin staining (original magnification, ×400). (B) Immunopositivity for CD99 in most tumor cells (original magnification, ×400). (C) No immunoreactivity for glial fibrillary acidic protein (original magnification, ×400). (D) Partial immunoreactivity for CD56 (original magnification, ×400).
series had leptomeningeal dissemination, the fact that this was not an autopsy series (such as Erlich and Davis9) may explain underdiagnosis of an often asymptomatic leptomeningeal dissemination.

In their series of high-grade gliomas, Arita et al.5 noted that overall survival after initial diagnosis was not significantly shorter in leptomeningeal dissemination but was markedly limited (mean 19 weeks) after dissemination was found. In their series of cerebellar GBMs, Tsung et al.17 reported median overall survival of patients with leptomeningeal dissemination was significantly shorter than in patients without dissemination, specifically 6.1 months versus 18.4 months.

Our case highlights an important discrepancy—the immunohistochemical pattern between the primary tumor and spinal metastasis, which showed no glial and only minor neuronal differentiation. We supposed that the different morphology was due to the distinct heterogeneity of GBM, similar to the variations shown by Sottoriva et al.21 in comparisons of several intratumoral samples from various locations. They demonstrated intratumor heterogeneity at the genotype, cellular phenotype, and single-molecule mitotic levels.21 However, another explanation may be the evolution of the tumor undergoing therapy as presented by Wang et al.,22 who found different transcriptional subtypes at diagnosis and relapse. These characteristics of GBM may represent the reason for treatment failure in these tumors.21,22

Given our patient’s history of leukemia during childhood, he was likely exposed to therapeutic ionizing brain radiation, which can pose an increased risk of developing brain cancer in adulthood.23,24 In patients with childhood acute lymphoblastic leukemia, Neglia et al.25 observed that the central nervous system (CNS) was the most common location for a secondary cancer. Postulating a correlation with treatment-related factors (especially radiation), they found an association between cancers of the CNS and hematopoietic cancers. Higher incidences of hematopoietic cancers among siblings of children with CNS tumors and vice versa have been reported; both CNS tumors and leukemias are part of Li-Fraumeni syndrome, an autosomal dominant disorder associated with abnormalities in the tumor protein p53 gene.25

CONCLUSIONS
Our patient with a supratentorial GBM with a primitive neuronal component developed spinal metastasis during the disease course that displayed features of dissemination similar to some of the latest findings reported in the literature. Immunohistochemical differences were observed between the primary tumor and spinal metastasis (the latter with no glial and minor neuronal differentiation), and spinal dissemination by leptomeningeal or ventricular invasion of the primary tumor was observed.

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Table 1. Pathologic Features of Primary Tumor and Spinal Metastasis

|            | GFAP | S100 | Vim | CD99 | CD56 | NeuN | Syn | NF | MAP2 | ATRX | IDH1 | CK | PS3 | Kif7 |
|------------|------|------|-----|------|------|------|-----|----|------|------|------|----|-----|-----|
| Temporal lobe tumor |     | +    | +   | +++  | +    | +    | +   | +  | +++  | -    | -    | +  | 50% |     |
| Spinal tumor    |     | -    | -   | +    | +    | +    | +   | -  | -    | ++   | -    | +  | 30% |     |

GFAP, glial fibrillary acidic protein; Vim, vimentin; Syn, synaptophysin; NF, neurofilament; MAP2, microtubule-associated protein 2; IDH1, isocitrate dehydrogenase 1; CK, cytokeratin.
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