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Spinal metastases of pineal region glioblastoma with primitive neuroectodermal features highlighting the importance of molecular diagnoses: illustrative case

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BACKGROUND Glioblastoma (GBM) is the most common primary brain tumor with poor patient prognosis. Spinal leptomeningeal metastasis has been rarely reported, with long intervals between the initial discovery of the primary tumor in the brain and eventual spine metastasis.

OBSERVATIONS Here, the authors present the case of a 51-year-old male presenting with 7 days of severe headache, nausea, and vomiting. Magnetic resonance imaging of the brain and spine demonstrated a contrast-enhancing mass in the pineal region, along with spinal metastases to T8, T12, and L5. Initial frozen-section diagnosis led to the treatment strategy for medulloblastoma, but further molecular analysis revealed characteristics of isocitrate dehydrogenase–wild type, grade 4 GBM.

LESSONS Glioblastoma has the potential to show metastatic spread at the time of diagnosis. Spinal imaging should be considered in patients with clinical suspicion of leptomeningeal spread. Furthermore, molecular analysis should be confirmed following pathological diagnosis to fine-tune treatment strategies.

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KEYWORDS glioblastoma; molecular profiling; leptomeningeal spread; spinal cord metastasis

Glioblastoma (GBM) is the most common primary brain tumor in adults, accounting for more than 50% of malignant primary brain tumors.[1] The prognosis for GBM patients is poor; despite aggressive surgical procedures, radiotherapy, and chemotherapy, disease progression is almost universal, with a median survival of less than 2 years.[2,3] Nearly all GBM tumors recur, with approximately 80% recurring within 2 cm of the primary site.[4]

Progression of disease outside of the brain is rare, typically found in the spinal cord, and associated with cerebrospinal fluid dissemination, known as leptomeningeal spread.[5] Spinal leptomeningeal metastasis in cases of GBM has been rarely reported, with long intervals between the initial discovery of intracranial GBM and metastatic spread.[6] Here, we report a case of an intracranial, pineal region GBM presenting with leptomeningeal spread to the thoracic and lumbar spine. The lesion was initially thought to be a pineoblastoma based on analysis of the frozen section. Further molecular analysis revealed the diagnosis of GBM. The case highlights the importance of molecular profiling to achieve accurate diagnosis of central nervous system tumors.

Illustrative Case

A 51-year-old man presented with 7 days of severe headache, nausea, and vomiting. The patient reported several months of intermittent, mild low-back pain in the lumbar area, followed by progressive hand and knee tremors. Upon neurological examination, subjective paresthesia was noted at the maxillary and mandibular distributions of the trigeminal nerve (V2 and V3). Magnetic resonance imaging (MRI) of the brain and spine demonstrated a contrast-enhancing mass in the pineal region with mild ventriculomegaly (Fig. 1). Leptomeningeal spread was also noted, with metastases to the thoracic and lumbar spine (Fig. 2).

To obtain a tissue diagnosis, biopsy of the L5 lesion was carried out via L4–5 laminectomy. Intraoperative frozen-section findings were

ABBREVIATIONS GBM = glioblastoma; IDH = isocitrate dehydrogenase; MRI = magnetic resonance imaging; TMZ = temozolomide.
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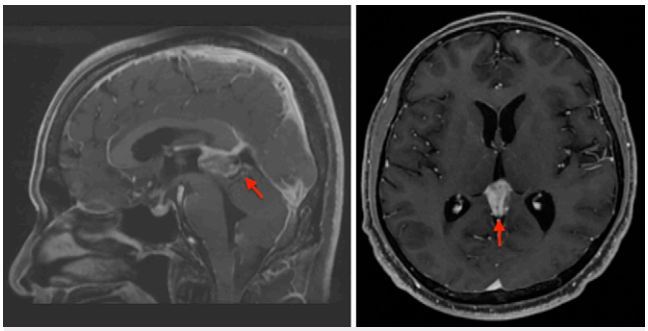

FIG. 1. Sagittal (**left**) and axial (**right**) magnetic resonance (MR) images of the brain at time of tumor diagnosis showing abnormal lesion in the pineal region *(red arrows)*.

consistent with metastatic pineoblastoma. The patient tolerated the procedure well. Histological analysis of permanent sections confirmed the diagnosis.

Pathological analysis showed a highly cellular neoplasm with mixed embryonal and glial features. Immunohistochemical analysis was nonspecific (glial fibrillary acidic protein (GFAP)+, synaptophysin+, epithelial membrane antigen- (EMA−), H3K27M−). The multidisciplinary tumor board recommended CyberKnife (Accuray, Inc.) radiosurgery, followed by craniospinal radiation therapy and chemotherapy regimen for pineoblastoma. The patient underwent CyberKnife treatment the following week, with treatment of the pineal tumor and the 3 spinal metastases at T8, T12, and L5 with a prescribed dosage of 1500 cGy across each of the 4 sites. Soon after, the patient underwent craniospinal radiation therapy at the same sites (36 Gy in 20 fractions).

However, following radiation therapy, molecular analysis and mutational profiling via next-generation sequencing revealed a diagnosis of GBM, isocitrate dehydrogenase (IDH)–wild-type, World Health Organization grade 4. This changed the recommended treatment strategy from chemotherapy regimen for pineoblastoma to monthly adjuvant temozolomide (TMZ). However, this was delayed due to

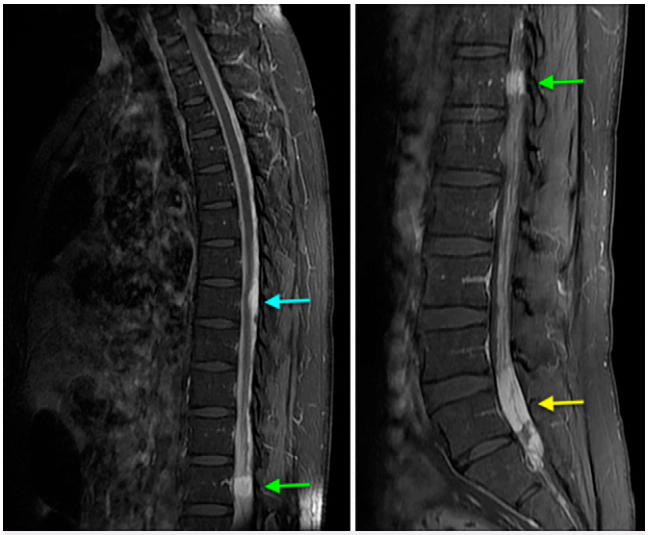

FIG. 2. Sagittal MR images of thoracic (**left**) and lumbar (**right**) spine with contrast at time of tumor diagnosis, demonstrating metastases to T8 (*blue arrow*), T12 (*green arrows*), and L5 (*yellow arrow*).

the patient's wish for vacation. He was prescribed a course of dexamethasone to prevent potential neurological decline in the interim. During his trip, the patient developed *Pneumocystis* pneumonia, for which a course of Bactrim and steroid treatment was completed. Avastin was then recommended as a safer regimen to avoid immunosuppression due to TMZ.

Following 6 cycles of Avastin, MRI showed a stable overall size of the pineal mass, although with increased enhancement. Disease progression was observed most significantly at the right cranial nerve III and the brainstem. Additionally, progression was observed in the spinal cord with new enhancing lesions at C3, T1–2, T3, and L3. At this point, the patient refused further treatment and was transferred to hospice. Five months later, 19 months after the initial discovery of the brain and spine lesions and 17 months after the diagnosis of GBM, the patient died.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

We present the case of a pineal GBM with primitive neuroectodermal features that metastasized to the spine. Usually, leptomeningeal spread occurs late in the disease course; however, imaging conducted during the initial presentation of the patient demonstrated both intracranial and spinal tumors. To our knowledge, this is the first case of intracranial GBM in the literature for which leptomeningeal spread to the spinal cord was seen at the time of the initial presentation. Thus, we believe that, in cases of suspected intracranial tumor, spine MRI should be considered, keeping in mind that spinal metastasis may occur with or soon after the initial GBM diagnosis.

In this case, the initial diagnosis of pineoblastoma was determined from an intraoperative frozen section during the laminectomy, which led to treatment with CyberKnife radiosurgery. However, on molecular analysis and further evaluation of the malignant tissue, the tumor was classified as a GBM, IDH–wild-type, grade 4 glioblastoma. Previous studies have evaluated the accuracy of frozen-section diagnosis, demonstrating that misclassification was a significant concern for GBM diagnosis.[7–10] Obeidat et al.[7] evaluated frozen-section diagnostic accuracy for brain tumors and found 3 cases in which the final GBM diagnosis differed from the frozen-section diagnosis, including 1 case of a small, round, blue cell tumor similar to the case presented here. Tumor-type misclassification was reported by other frozen-section diagnosis accuracy evaluations, especially in the case of misinterpreting gliomas as other nonglial tumors, including primitive neuroectodermal tumor and metastatic carcinoma.[8–10] This demonstrates the importance of further molecular analysis following frozen-section diagnosis. While there is a need to proceed to treatment as soon as possible, waiting for final molecular analysis can help fine-tune the treatment protocol.

The median survival times of patients after the diagnosis of intracranial GBMs and after the diagnosis of leptomeningeal metastasis are 11–17 months and 2–3 months, respectively.[11] In this case, the patient died 17 months after the discovery of spinal and intracranial lesions. Even after systemic combination of chemotherapy and radiosurgery, survival and neurological function have not improved for patients with GBM.[12] Following the combination of chemotherapy

and CyberKnife radiosurgery, the patient's tumor recurred within 8 months of the initial diagnosis. There remains a need to develop advanced therapeutic options to treat GBMs.

Lessons

This unique case provides valuable insights about the histological presentation of GBM. Multidisciplinary management teams should be aware of potential leptomeningeal metastasis, conducting complete MRI of both the brain and spinal cord. Moreover, complete molecular profiling is important to guide treatment strategies for pineal region tumors, especially when initial diagnoses are nonspecific.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Shah, Marianayagam, Park, Persad, Veeravagu. Acquisition of data: Shah, Marianayagam, Persad. Analysis and interpretation of data: Shah, Marianayagam, Persad, Chang. Drafting of the article: Shah, Marianayagam, Persad. Critically revising the article: all authors. Reviewed submitted version of the manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Shah. Administrative/technical/material support: Shah, Park. Study supervision: Park.

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