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CASE REPORT

Extracranial metastasis of pediatric glioblastoma: case report and literature review

Wei-Zhi Huang[1] · Hung-Chieh Chen[2,3] · Te-Kau Chang[4] · Weir Chiang You[5] · Yee-Jee Jan[6] · Yu-Cheng Chou[7,8,9,10]

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Abstract

Glioblastoma (GBM) is a rare primary brain tumor in children, and extracranial metastases of pediatric GBM are particularly uncommon. We present the case of a 10-year-old girl with pediatric GBM who developed multiple extracranial metastases, including cervical lymph nodes, spine, and lung. We discuss the rarity of extracranial metastases in GBM and explore possible mechanisms of dissemination. The patient underwent surgical resections, radiotherapy, and chemotherapy, but the metastatic disease progressed despite treatment. We emphasize the need to consider extracranial metastases in pediatric GBM patients and adopt multimodal treatment approaches for managing this rare clinical entity. As the survival rates of pediatric GBM patients are improving, awareness of extracranial metastases is crucial for optimizing treatment outcomes.

Keywords Glioblastoma · Pediatric · Extracranial metastases · Lymph nodes · Spine · Lung · Multimodal treatment

Introduction

Glioblastoma (GBM) is a primary brain tumor that is rare in children, accounting for only 3–15% of pediatric central nervous system tumors [1]. Despite its rarity, pediatric GBM is a devastating disease with a median survival duration ranging from 13 to 73 months and a 5-year survival rate of less than 20% [2–4]. Extracranial metastases were reported in 0.4–0.5% of all glioblastomas, and cases of extracranial metastases in pediatric GBM are especially rare [2–4]. In the literature, leptomeningeal spreading or extension via surgical path explains most metastases [5, 6]; however, more than 10% of extracranial metastases occur in patients without prior operation [7]. To the best of our knowledge, the patient described herein is the third reported case of pediatric GBM with multiple extracranial metastases and the second case of pediatric GBM with metastasis to cervical lymph node [8]. The literature is reviewed, and the possible pathophysiology is discussed.

Case report

A 10-year-old girl presented with a history of headaches and dizziness for 2 months. Magnetic resonance imaging (MRI) of the brain revealed a cystic tumor in the left parieto-occipital region (Fig. 1). The patient underwent craniotomy for tumor removal, and pathological examination

✉ Yu-Cheng Chou
chouycns@yahoo.com.tw

1 Department of Medical Education, Taichung Veterans General Hospital, Taichung, Taiwan

2 Department of Radiology, Taichung Veterans General Hospital, Taichung, Taiwan

3 School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

4 Section of Pediatric Hematology, China Medical University Children's Hospital, Taichung, Taiwan

5 Department of Radiation Oncology, Taichung Veterans General Hospital, Taichung, Taiwan

6 Department of Pathology and Laboratory Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

7 Department of Neurosurgery, Neurological Institute, Taichung Veterans General Hospital, No.1650, Sec. 4, Taiwan Blvd., Taichung 407, Taiwan

8 Department of Applied Chemistry, National Chi Nan University, Nantou, Taiwan

9 Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan

10 Department of Neurological Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

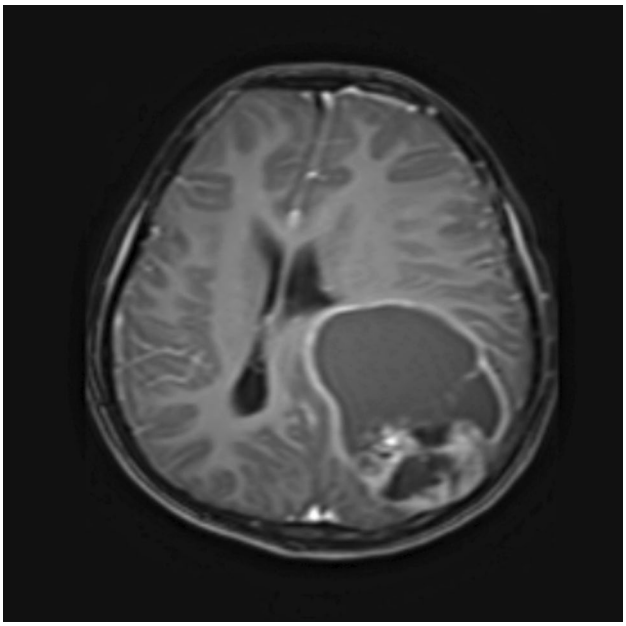

Fig. 1 T1-weighted MRI of the brain with gadolinium enhancement demonstrating an ill-defined cystic mass, 6.5 cm in diameter, with a heterogeneous enhancing nodule, around 4.2 cm in diameter, in the left parieto-occipital region in axial view

confirmed the diagnosis of glioblastoma. As there were no standards for adjuvant chemotherapy in pediatric high-grade glioma patients, the treatment decisions were made by our pediatric neuro-oncology team based on limited literature [9, 10].

The patient received adjuvant concurrent chemoradiotherapy (CCRT) with radiotherapy, 6.9 Gy in 30 fractions, temozolomide for 42 days, followed by monotherapy with temozolomide. Her dizziness improved initially, but she developed low back pain 4 months after the first surgery. MRI of the spine showed a compression fracture with an enhanced lesion at the L1 level (Fig. 2), which was confirmed to be an osteolytic bone metastasis of glioblastoma by whole body bone scan with single photon emission computed tomography/computed tomography (SPECT/CT) (Fig. 3). The patient underwent percutaneous transpedicular biopsy, and pathological examination disclosed glioblastoma with immunohistochemistry (IHC) stains with S-100 (+), epithelial membrane antigen, EMA (focal+), glial fibrillary acidic protein, GFAP (+), cytokeratin AE1/AE3 (−), and INI-1 (understaining).

Five months after the first craniotomy, the child experienced vertigo and aphasia. MRI of the brain showed recurrence of the cystic tumor. She underwent craniectomy with tumor removal and received bevacizumab (Avastin) in combination with temozolomide, as well as additional radiotherapy for spinal metastases and recurrent brain tumor bed. However, her low back pain worsened, and MRI of the brain demonstrated an enlarged neck lymph node (Fig. 4). The presence of glioblastoma in neck lymph nodes was pathologically confirmed through IHC stains, showing positive expression of GFAP (focal+) and INI-1 (+).

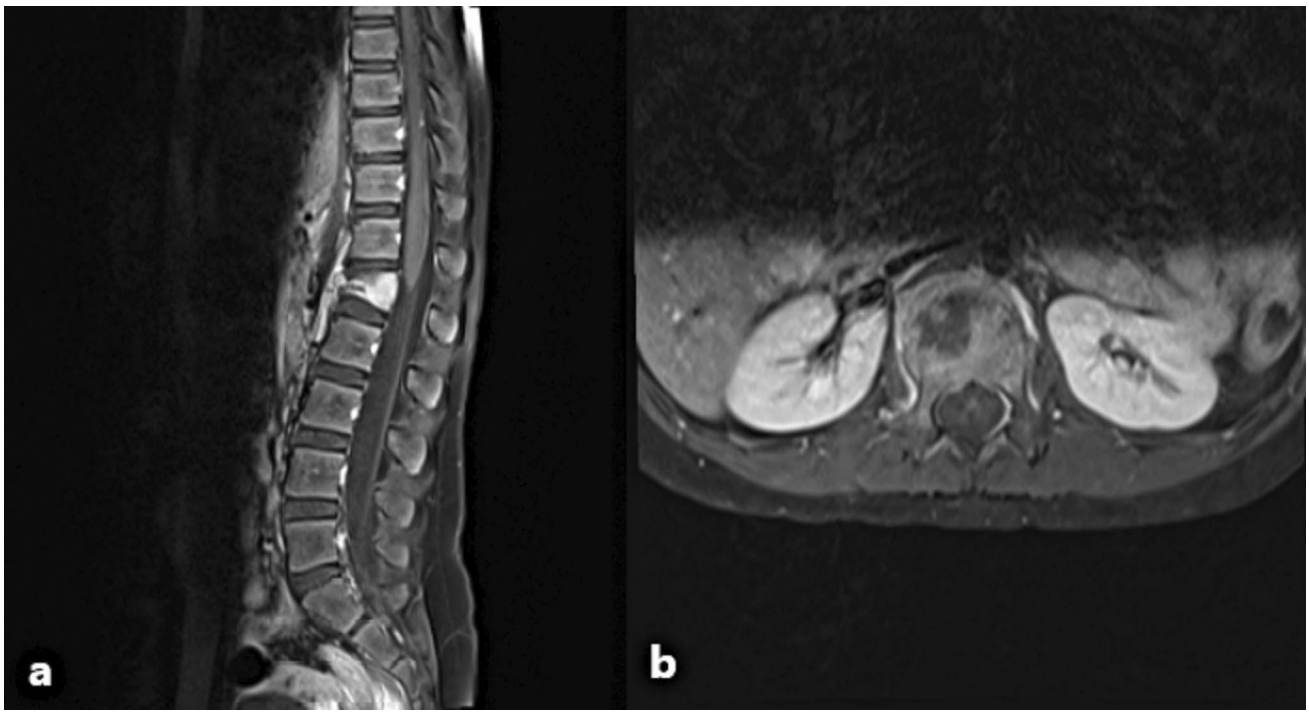

Fig. 2 T1-weighted MRI of the spine with gadolinium enhancement showing wedge-shaped compression fracture at the vertebral body of L1 level with retropulsion of bony fragment causing anterior indentation to the dura sac in sagittal view (**a**) and axial view (**b**)

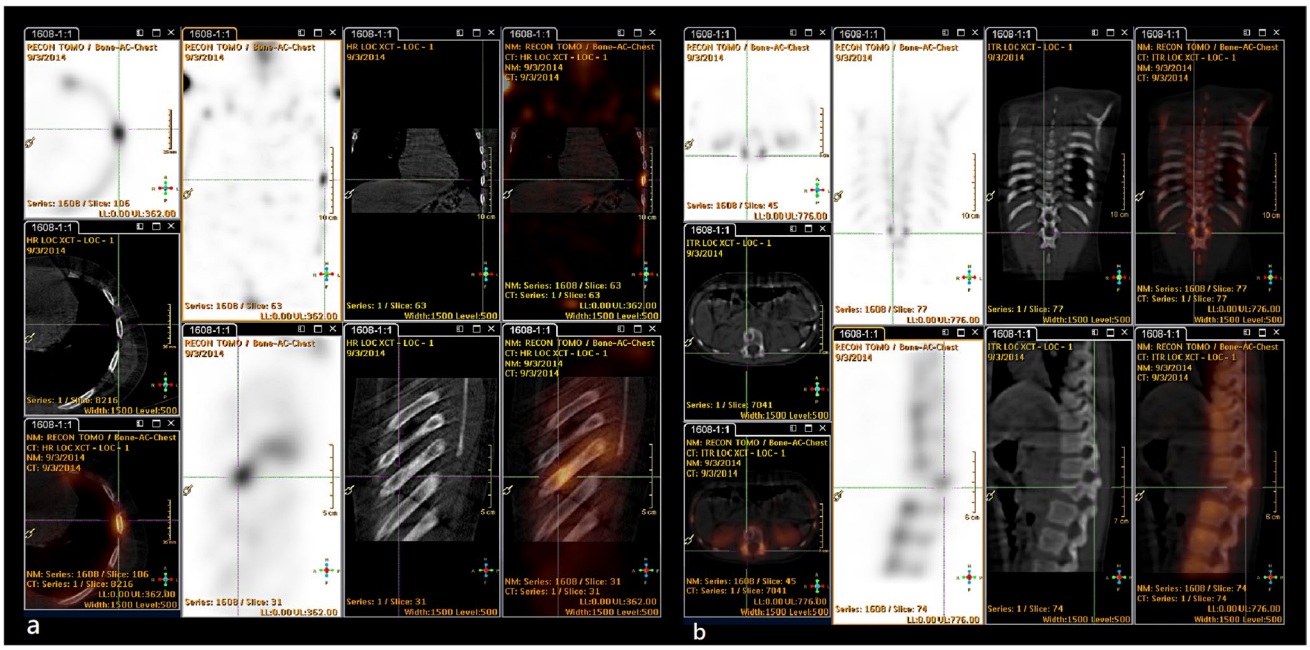

Fig. 3 Whole-body bone scan with Tc-99 m methylene diphosphonate (Tc-99 m MDP) and SPECT/CT revealing increased MDP uptake in the lateral aspect of left 6th rib (**a**), decreased MDP uptake in the vertebral body of L1 level, and mildly increased MDP uptake at the bilateral superior articular processes of L1 level (**b**)

However, the patient developed chest pain 8 months after the first surgery, and CT revealed lung metastasis. Ten months after the first craniotomy, she experienced generalized tonic clonic seizure, and brain CT showed contralateral cerebral hemisphere involvement by the tumor. Finally, she received hospice care and succumbed to pneumonia 11 months after the first brain surgery.

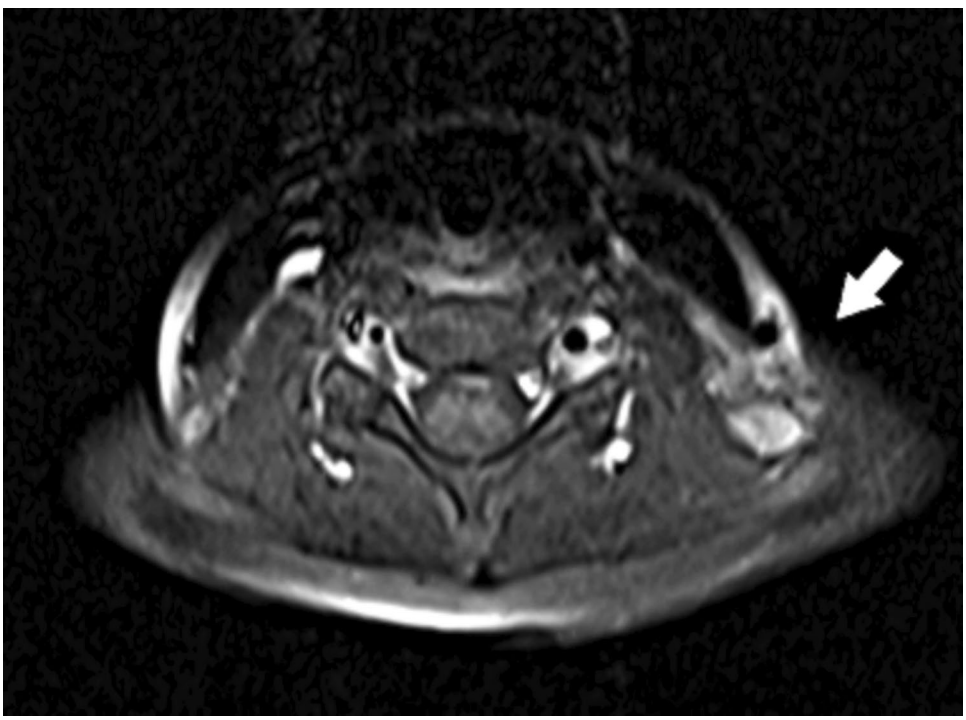

Fig. 4 T1-weighted MRI of the brain with gadolinium enhancement showing an enlarged lymph node (white arrow) over left lower neck in axial view

Discussion

Extracranial dissemination of glioblastoma to lung, chest wall, and soft tissue of an arm was first reported in 1928 [11]. With advances in treatment, more cases of extracranial metastases in pediatric GBM have been reported. Our case adds to the literature on the metastatic potential of pediatric GBM. Understanding the mechanism of extracranial metastases is essential for improving treatment outcomes.

Several hypotheses have been put forward to explain why extracranial metastases of glioblastoma are so rare. Lun et al. described several biological factors that may prevent tumor cells from infiltrating the neural environment, including the lack of a lymphatic system in the brain and spinal cord, the dense dura surrounding intracranial veins, and the absence of adequate nurturing stroma in other organs to support the proliferation of glioblastoma cells [2].

In the literature, leptomeningeal spreading or extension via surgical path explains most metastasis [5, 6]. Reports have identified cases of leptomeningeal dissemination, essentially diagnosed on imaging studies [12]. The seeding of glioblastomas along the track of the ventriculoperitoneal shunt has also been reported, with the potential route being CSF shunting [13]. Hematogenous circulating tumor cells (CTCs) were found in the peripheral blood of 29 out of 141 (20.6%) GBM patients. Immunostaining of enriched mononuclear cells with antibodies targeting glial fibrillary acidic protein (GFAP) was used for detection. This finding suggests that the hematogenous spread of GBM is an inherent characteristic of its biology [14].

Cervical lymph nodes are the second most common locations of extracranial metastases in the glioblastoma according to the literature [8]. This is presumably because they are in the vicinity of the surgical site. Nonetheless, pediatric cases with extracranial metastases are rare. The lymphatic fluid channels along the cranial nerves and vascular structures were found to be directly connected to the cervical lymph nodes by non-invasive MR imaging in a recent report, which may explain the occurrence of cervical metastases in pediatric GBM [15]. In summary, the possible routes of extracranial metastases of pediatric GBM include leptomeningeal, hematogenous, and lymphatic dissemination, as well as CSF shunting.

There is no current standardized protocol for the management of extracranial metastases of gliomas. No significant difference in clinical efficacy has been found between radiotherapy and/or chemotherapy in most patients [16, 17]. Our patient underwent two brain surgeries and open spine surgery, and received radiotherapy for both the brain tumor bed and spinal metastases. Our surgery debulked her tumor volumes, improved her vertigo and aphasia, stabilized her spine structures, and improved her neurological functions in walking; radiotherapy relieved her low back pain and benefited her walking; however, the ability of chemotherapy to slow down the progression of multiple metastases in our patient was limited.

In conclusion, we describe the case of a female pediatric patient who developed multiple extracranial metastases involving lymph nodes, spine, and lung. Based on our literature review, the patient described herein is the third case of pediatric GBM with multiple extracranial metastases and the second case of pediatric GBM with metastasis to cervical lymph node. With the increasing survival rates of pediatric GBM patients, it is anticipated that the occurrence of this rare clinical entity will also increase. It is important to keep extracranial metastases in mind if a patient has lesions at different sites and to adopt multimodal approaches in the management of such patients.

Author contribution Wei-Zhi Huang, Hung-Chieh Chen, and Yu-Cheng Chou conceptualized and drafted the manuscript. Hung-Chieh Chen also edited the manuscript. Yu-Cheng Chou revised the manuscript and supervised the research work. Te-Kau Chang reviewed the literature and performed chemotherapy. Weir Chiang You reviewed the literature and performed radiotherapy. Yee-Jee Jan made the histopathologic diagnosis and reviewed the literature.

Data availability All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital (IRB: CE19140B).

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

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