

Multiple extracranial metastases from secondary glioblastoma multiforme: a case report and review of the literature

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Abstract Extracranial metastasis of glioblastoma multiforme (GBM) is very rare, in spite of very aggressive tumor behavior and being documented in only a few patients. In this article we present a 25-year-old man with secondary glioblastoma associated with extracranial progression and distant metastasis. He was diagnosed by magnetic resonance (MR) with an intracranial lesion in the right parietofrontal region, which was subsequently resected. Histology revealed a diffuse astrocytoma (grade II). The tumor recurred 1 year later and the patient received a second craniotomy. A diagnosis of GBM was made. After radiotherapy, he presented with right cervical lymph node metastases. The cytomorphological features supported a diagnosis of metastatic glioblastoma multiforme. The neck dissection was made and histology confirmed the fine needle aspiration diagnosis of glioblastoma multiforme. MR with diffusion-weighted imaging revealed right cervical lymph node metastases and multi-bone metastases (mainly pelvic bone) 3 weeks later.

Keywords Glioblastoma multiforme · Extracranial metastasis · Secondary glioblastoma · Prognosis

Introduction

Glioblastoma multiforme is a highly aggressive intracranial malignant tumor and has the highest fatality rate of all primary central nervous system (CNS) malignancies [1]. The prognosis remains very poor, with most patients dying within 1 year after diagnosis. Glioblastomas may develop de novo (primary glioblastomas) or through progression from low-grade or anaplastic astrocytomas (secondary glioblastomas). Primary and secondary glioblastoma constitute distinct disease subtypes, affecting patients of different age and developing through different genetic pathways. Secondary glioblastomas evolve slowly through progression from low-grade diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). Glioblastomas usually spread by local growth and infiltration. Extracranial metastasis of this tumor is very rare, despite its highly malignant nature. We report a case of secondary glioblastoma that metastasized to the right cervical lymph nodes and bone.

Case report

A 25-year-old man had a 10-day history of left facial and upper limb anesthesia. On neurological examination, the myodynamia of the left upper limb was IV. Magnetic resonance (MR) showed a right parietofrontal lobe mass measuring $5 \times 4.6 \times 4$ cm with long T1 and long T2 signal (Fig. 1). The verge of the tumor was well defined without obvious peritumoral edema. A nodular-enhanced mass was identified in the right parietal lobe (Fig. 1). Craniotomy was performed with gross total resection on October 8, 2007. Upon macroscopic examination of the operation material, there were many tissue specimens,

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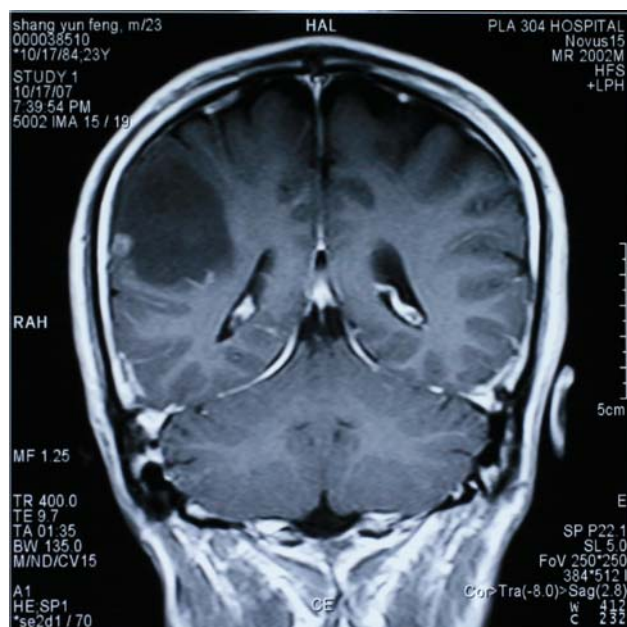


Fig. 1 Gd-enhanced coronal T1-weighted MR images before first operation demonstrating a nodular-enhanced mass in the right parietofrontal region

Fig. 2 Pathologic findings of first operation showing diffuse astrocytoma (WHO grade II) (left: H&E, $\times 200$; right: H&E, $\times 400$)

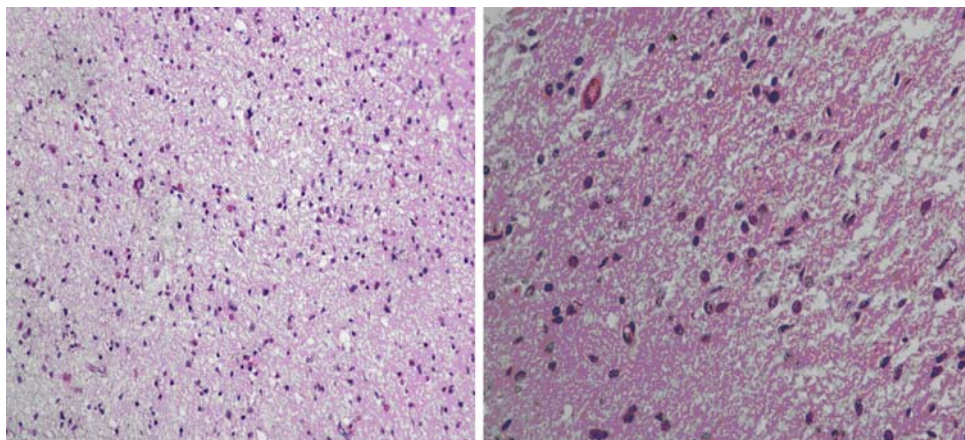
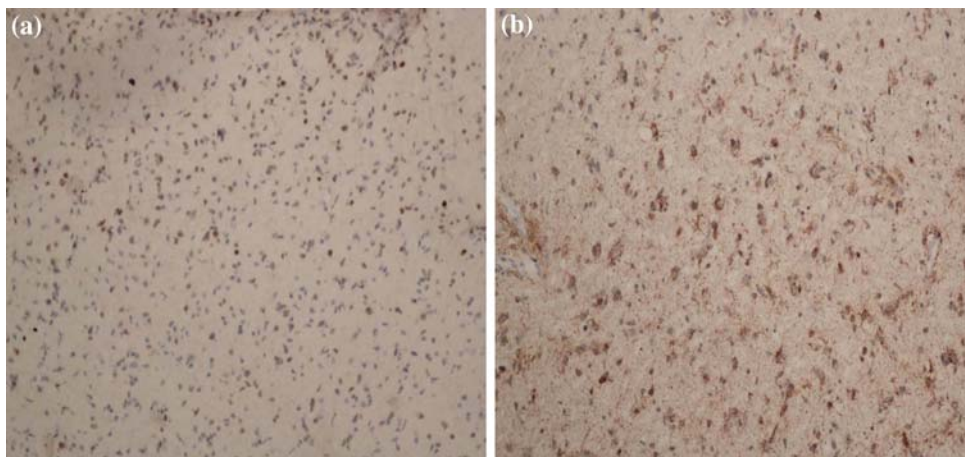


Fig. 3 Biopsy specimen taken from the first craniotomy showing immunopositive cells for p53 (a), EGFR (b) ($\times 200$)



measured together $7 \times 6 \times 4$ cm. These tissue specimens were hemorrhagic, irregular, soft and grey–white on the cut surface. The histopathological diagnosis reported a diffuse astrocytoma (grade II) (Fig. 2). The patient did not take any adjuvant therapy after surgery. Immunohistochemical results showed that the tumor cells were weakly positive for p53 and epidermal growth factor receptor (EGFR) (Fig. 3).

One year later, the patient was admitted to the hospital on November 9, 2008, complaining of weakness in left arm, and left hemiparesis. MR showed a recurrent lesion at the location of the first operation, $4 \times 3 \times 2$ cm in diameter with clear dense contrast enhancement (Fig. 4). The tumor was homogeneous post-gadolinium enhancement with surrounding edema. A second craniotomy revealed a malignant neoplasm on frozen section and on final pathological evaluation and a diagnosis of GBM was made (Fig. 5). Pathological examination of the second operation material revealed the tissue specimens together measured $3 \times 3 \times 1.5$ cm. The tissue specimens were soft and grey on the cut surface just the same as those in the first operation. Pathological studies revealed that there was no

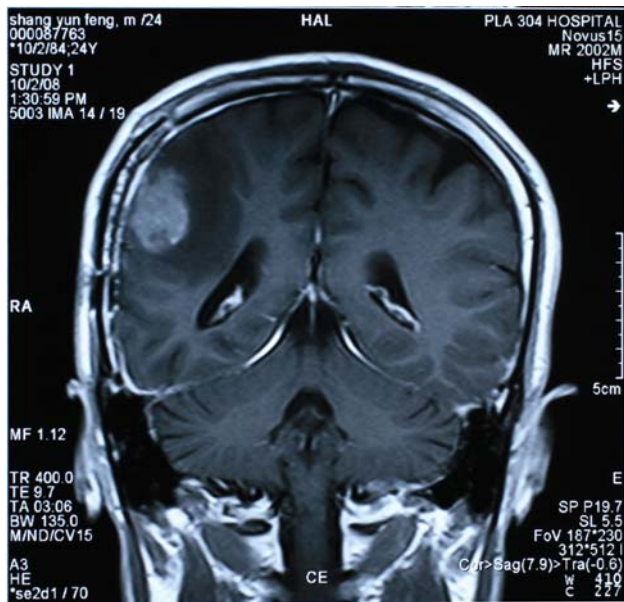


Fig. 4 Gd-enhanced coronal T1-weighted MR images of the brain before the second operation revealing a recurrence at the location of the first operation with patchy surrounding edema

Fig. 5 Pathologic findings of the second operation revealing intracranial glioblastoma with variable histologic features, mitosis, endothelial proliferation, and necrosis (*left*: H&E, $\times 100$; *right*: H&E, $\times 400$)

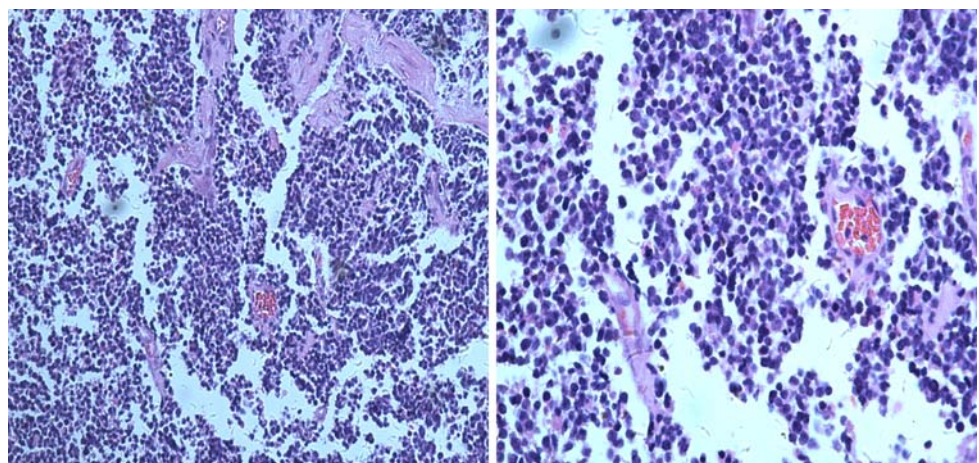
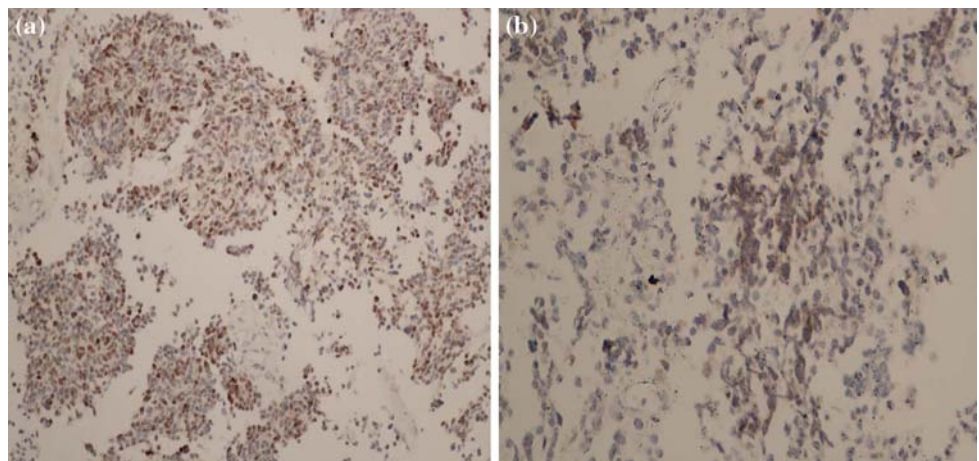


Fig. 6 Biopsy specimen taken from the second craniotomy showing immunopositive cells for p53 (a), EGFR (b) ($\times 200$)



mesenchymal formation with typical sarcomatous components, which were composed of spindle-shaped sarcomatous elements. Immunohistochemical results showed that the tumor cells were positive for p53, EGFR (Fig. 6), O-6-methylguanine-DNA methyltransferase (MGMT), syn, CD56, Ki-67, negative for CD3, CD99, glial fibrillary acidic protein (GFAP), S-100, vascular endothelial growth factor (VEGF), Vimentin, Leu-7, Olig-2, Nestin, Neu-N. The patient was treated with 5100 cGy/17F of external beam radiation therapy after surgery.

Two months later, the patient returned with a 2.0-cm subcutaneous mass in the right cervical. There was no improvement with antibiotics for 7 days. Contrast-enhanced computerized tomography (CT) showed that there was extensive adenopathy in the deep cervical (Fig. 7). Fine-needle aspiration biopsy revealed a GBM (Fig. 8). Neck dissection was made 1 month later with histological confirmation of the diagnosis and 22 lymph nodes were found tumor invasive of total 27 resected lymph nodes (Fig. 9). Immunohistochemically, the tumor cells were strongly positive for p53, EGFR (Fig. 10) and

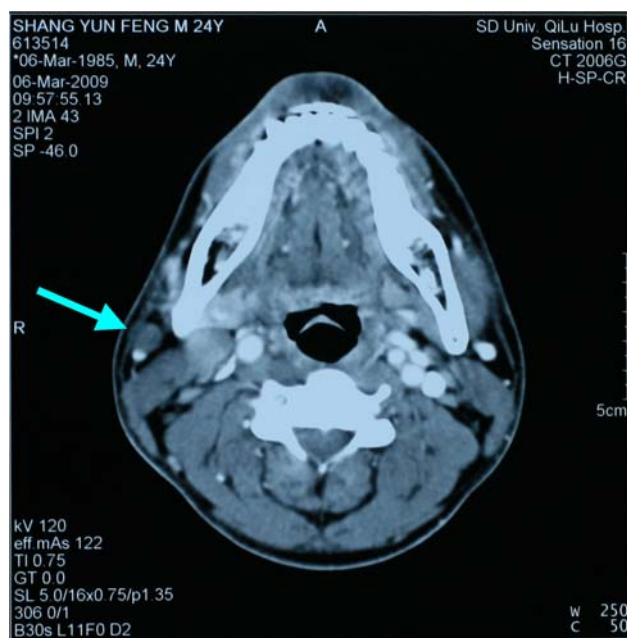


Fig. 7 Contrast-enhanced transaxial CT showing lymph node in right cervical area (arrow)

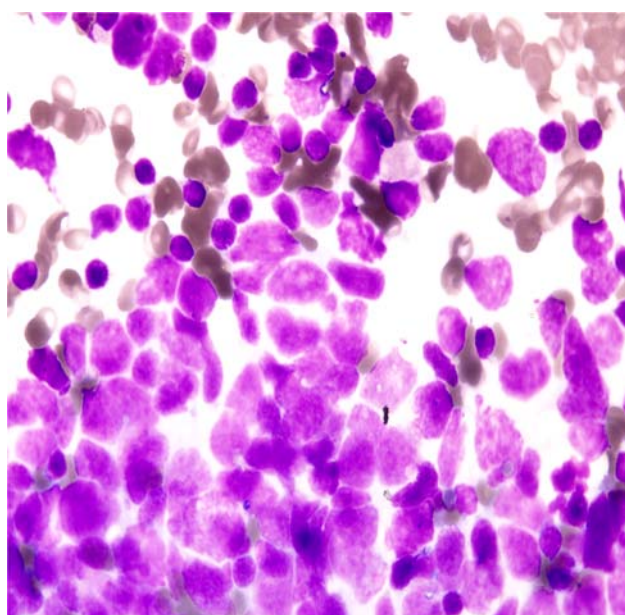


Fig. 8 Fine-needle aspiration smear from metastatic glioblastoma in cervical lymph node. Photomicrograph shows that metocyte infiltrated into the lymphocytes in the cervical soft tissue (H&E, $\times 1000$)

syn, the same as that of the second craniotomy. We also determined S100 (Fig. 10), epithelial membrane antigen (EMA), and Vimentin immunodetection, which represent sarcomatous components in these samples. None of them was positive. The other immunohistochemical findings revealed that the tumor cells were negative for GFAP, CK, CD2, CD35, CK19, smooth muscle actin (SMA), and

Desmin. The diagnosis of gliosarcoma was excluded since reticulin stains disclosed a little reticulin fiber around the nests of tumor rather than the tumor cells (Fig. 11).

Two lymph nodes were found again in the right cervical 3 weeks later. MR with diffusion-weighted imaging revealed right cervical lymph node metastases and multi-bone metastases (mainly pelvic bone) (Fig. 12). The patient is currently in the hospital again ready to receive systemic chemotherapy.

Discussion

The diagnosis of secondary glioblastoma requires clinical (neuroimaging) or histological (bioptic) evidence of a development from a less malignant astrocytoma. In this article, the secondary glioblastoma was confirmed by clinical, morphological, and histological studies. According to the studies, only 5% of all glioblastomas were secondary glioblastomas with histopathological evidence of a precursor low-grade or anaplastic astrocytoma [2, 3]. The median survival of secondary glioblastoma patients was 7.8 months, significantly longer than that of primary glioblastoma patients (4.7 months; $P = 0.003$). The patient in our case report has survived for 17 months since the first operation.

It is widely known that secondary glioblastoma occurs with LOH on chromosome 17p strongly correlated with *p53* mutations and is often seen in younger patients, whereas primary glioblastoma is characterized by higher frequencies of EGFR amplification and LOH on chromosome 10 and is common in older patients. It has been reported that mutations of *p53* occur in more than 65% of secondary GBM samples [4], such mutations were seen in all samples of our case obtained at three operations. However, immunopositive for EGFR were also observed in our case. The *p53* mutation with concomitant EGFR gene amplification was hardly observed in secondary glioblastomas. However, Yoon KS et al. reported immunoreactivities for EGFR were noted in 66.7% of primary glioblastomas and in 9.5% of secondary glioblastomas [5]. Watanabe et al. reported that only one out of 20 secondary glioblastomas showed the *p53* mutation with concomitant EGFR overexpression [6]. In the present case, *p53* was weakly positive in the samples obtained at the first operation and strongly positive in the samples obtained at the second operation and neck dissection, EGFR was also positive in all samples, but the positive rates were increased at the third operation. To our knowledge, it is the first report of a secondary glioblastoma with EGFR overexpression and the *p53* mutation associated with multiple extracranial metastases.

Glioblastoma multiforme can easily metastasize to the neuroaxial (meninges or spinal cord) spread by way of the

Fig. 9 Pathologic findings of biopsy specimen taken from neck dissection, confirmed as glioblastoma (*left*: H&E, $\times 100$; *right*: H&E, $\times 400$)

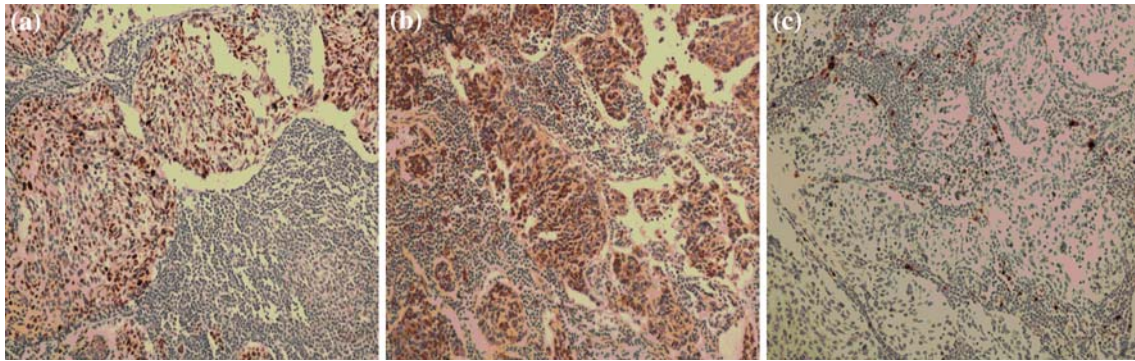
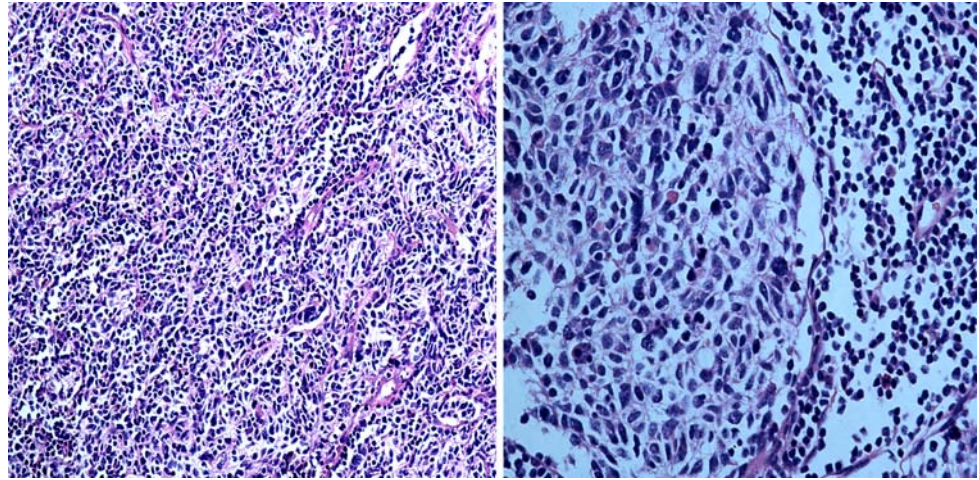


Fig. 10 Biopsy specimen taken from neck dissection showing immunopositive cells for p53 (a), EGFR (b), and immunonegative cells for S100 (c) ($\times 200$)

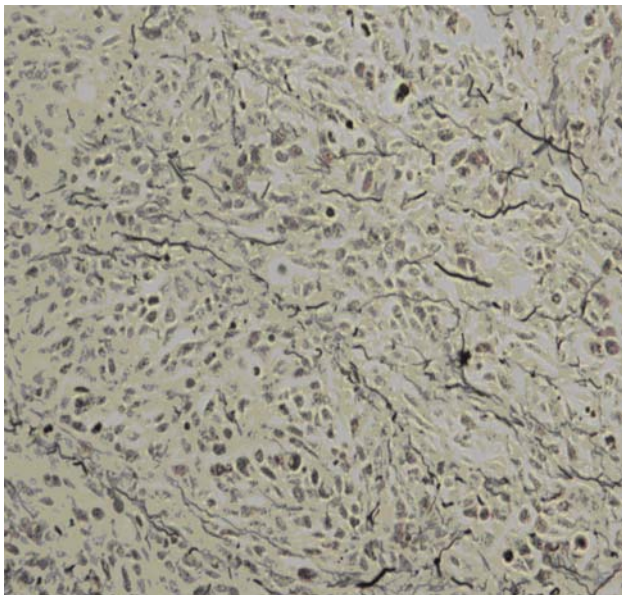


Fig. 11 Reticulin stains disclosed a few reticulin fiber around nests of tumor rather than tumor cells ($\times 400$)

cerebrospinal fluid (CSF), but extracranial metastases are much rarer. Based on the findings of autopsies, the incidence of CSF spread in glioblastomas was about 20% [7, 8]. Although extracranial metastases of glioblastomas occur in <1% of cases, glioblastomas account for about two-thirds of the neuroepithelial tumors that metastasize extracranially [9]. The lungs, pleura, lymph nodes, bone marrow, bone, and liver are the most common sites of extracranial metastases. In a review of literature of extracranial metastases of astrocytomas and glioblastomas, distribution of metastasis was as follows: 43 (59.7%) lungs and pleura, 37 (51.4%) lymph nodes, 22 (30.5%) bone, 16 (22.2%) liver, five heart, three adrenal gland, two each in the kidneys, diaphragm and mediastinum and one each in the pancreas, thyroid gland, and peritoneum [10]. Among the lymph node metastases, 62% were situated in the cervical areas, often ipsilateral to the site of craniotomy but sometimes bilateral [10]. In our case report, ipsilateral cervical lymph node metastases were found in the patient. It recurred in the ipsilateral cervical after neck dissection, and the contralateral cervical remained negative. Regarding bone metastases, the vertebral spine

Fig. 12 Whole-body MR with diffusion-weighted imaging revealed right cervical lymph node metastases and multi-bone metastases (mainly pelvic bone) (arrows)



(73%) was the most common site of involvement, followed by the ribs (23%), sternum (18%), skull (14%), and acetabulum (9%) [10]. However, our patient in this case showed pelvic diffuse bone involvement.

The exact mechanism of metastases is still not well understood, although several hypotheses have been advanced and some experimental studies have been performed. Extracranial metastases of glioblastomas usually occur after surgery in which the tumor cells may find an access to the lymphatics via dural or scalp extension through the surgical defect [11]. The tumor can also spread extracranial through the opening of the intracerebral vessels with surgical intervention [12]. Spreading to the peritoneum via shunts is the third most common metastatic pathway [13]. Our patient developed right cervical lymph node metastases and bone metastases at the same time after second craniotomy. The pathways of extracranial metastases in our case may include lymphatic spread and hematogenous spread of glioblastoma.

However, these mechanisms do not account for the occurrence of extraneural metastases in all patients, because there are cases of extracranial metastases of glioblastoma without previous surgical intervention [14–16]. These cases might be interpreted as a CSF or blood spreading of tumor cells. It seems probable that the glioblastoma spreads outside the skull through the venous

system, after having gained entrance to it either at the dural or intracerebral level [17].

Management of glioblastoma usually includes surgical excision, followed by radiation therapy. Sometimes chemotherapy is given in combination with radiation or as an adjuvant treatment either before or after surgery [1, 18]. Particularly in young patients a combined triple therapy can prolong the time of survival significantly. Soft-tissue metastases sometimes decrease in size in dramatic fashion with systemic chemotherapy [19]. We decided to introduce chemotherapeutic agents to this patient because the tumor has scattered extensively. Being a highly aggressive malignant tumor, the prognosis of glioblastomas is very poor, even though surgical procedure, radiation therapy, and chemotherapy are all used.

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