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Case report

Extracranial metastasis of glioblastoma: A case report and literature review

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ABSTRACT

Introduction: Glioblastoma (GBM) is the most common malignant tumor of the central nervous system. Extracranial metastasis is rare, accounting for only 0.4 %–0.5 % of all GBM patients. The pathways and mechanisms involved are still unclear.

Case presentation: We reported a rare case of GBM with multiple bone metastases, highly suspected of abdominal metastasis. This 20 year old woman underwent surgery in March 2017 and underwent postoperative radiotherapy and chemotherapy. In July 2018, she underwent a second surgery due to intracranial recurrence and also underwent radiotherapy and chemotherapy after the surgery. She experienced pain in the lumbosacral region in May 2019, abdominal magnetic resonance imaging (MRI) showed metastases to the ilium, sacrum, and multiple lumbar vertebrae. In August 2019, a lump was discovered at the sternum and biopsy was performed, pathological examination confirmed it as GBM. During this period, the patient's condition was briefly controlled after receiving palliative radiotherapy, chemotherapy, and targeted treatment. Surprisingly, the patient later developed highly suspected malignant ascites, and further anti-tumor treatment was refused. She died 7 months after diagnosis of extracranial metastases.

Clinical discussion: This patient with GBM had multiple bone metastases and highly suspected abdominal metastasis after two operations. Chemotherapy, radiotherapy and Targeted therapy extend the survival period and improve the quality of life.

Conclusion: We believe that the patient's extracranial metastases may have occurred through blood. Young "long-term survivors" who have undergone surgery seem to have a higher risk of extracranial metastasis. Timely detection and early treatment can improve the overall quality of life of the patient.

1. Introduction

Glioblastoma (GBM) is the most common central nervous system malignancy in adults, with a median survival time of about 14.6 months. Most patients experience local progression during the course of the disease, and extracranial metastasis (ECM) is rare, with an estimated incidence of 0.4 %–0.5 % and the most frequent sites of involvement being lungs, pleura, lymph nodes, bone marrow, bone, and liver [1]. In recent years, ECM cases have been reported successively in the literature, but the specific cause and mechanism have not yet been identified. Here, we report a case of ECM of GBM. This work has been reported in line with the SCARE 2020 criteria [2].

2. Case report

In February 2017, a 20-year-old female complained of "headache for two months" and had a head magnetic resonance image (MRI) performed in another hospital (Fig. 1). A large area of abnormal mixed signals can be seen in the left temporal lobe, and the focus is significantly enhanced after enhanced scanning considering the possibility of glioblastoma. Then, in March 2017, a near-total intracranial tumor resection was performed in another hospital. The postoperative pathological diagnosis was glioblastoma (World Health Organization (WHO) grade III–IV) . Immunohistochemical detection identified several molecular features (Fig. 2), such as p53 gene mutation and positive glial fibrin acid protein (GFAP).

After the operation, she was admitted to our hospital for diagnosis

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and treatment. The head MRI showed that there was a patchy, abnormal signal shadow in the operation area of the left temporal and occipital lobes with a size of about 4.0 × 2.5 cm. The patient underwent treatment consisting of radiotherapy at a total dose of 60 Gy in 30 divided fractions with concurrent daily temozolomide (75 mg/m^2 of body surface area), followed by 10 cycles of adjuvant temozolomide (150 mg/m^2) for 5 days every 28 days. During this period, head MRI confirmed that the condition was stable, chest X-ray examination showed no metastasis. In April 2018, the patient complained of headaches. A new head MRI showed that the original left temporal-occipital lobe-shaped abnormal signal shadow was the same as before, but there was a growing nodule anterior to it, and tumor recurrence was considered. Oral chemotherapy with temozolomide was continued. In June 2018, an additional head MRI was administered and examined; the original lesion in the left temporal and occipital lobes was the same as before, and the recurrent tumor below it was larger (still accompanied by surrounding edema). In July 2018, another partial resection was performed in another hospital. Preoperative examination revealed no metastasis in the chest, the patient's headache symptoms were relieved after surgery. Postoperative pathological diagnosis was glioblastoma, WHO grade IV, confirmed as intracranial recurrence. In July 2018, the patient moved to our hospital; two courses of "temozolomide 150 mg d 1–7" chemotherapy every other

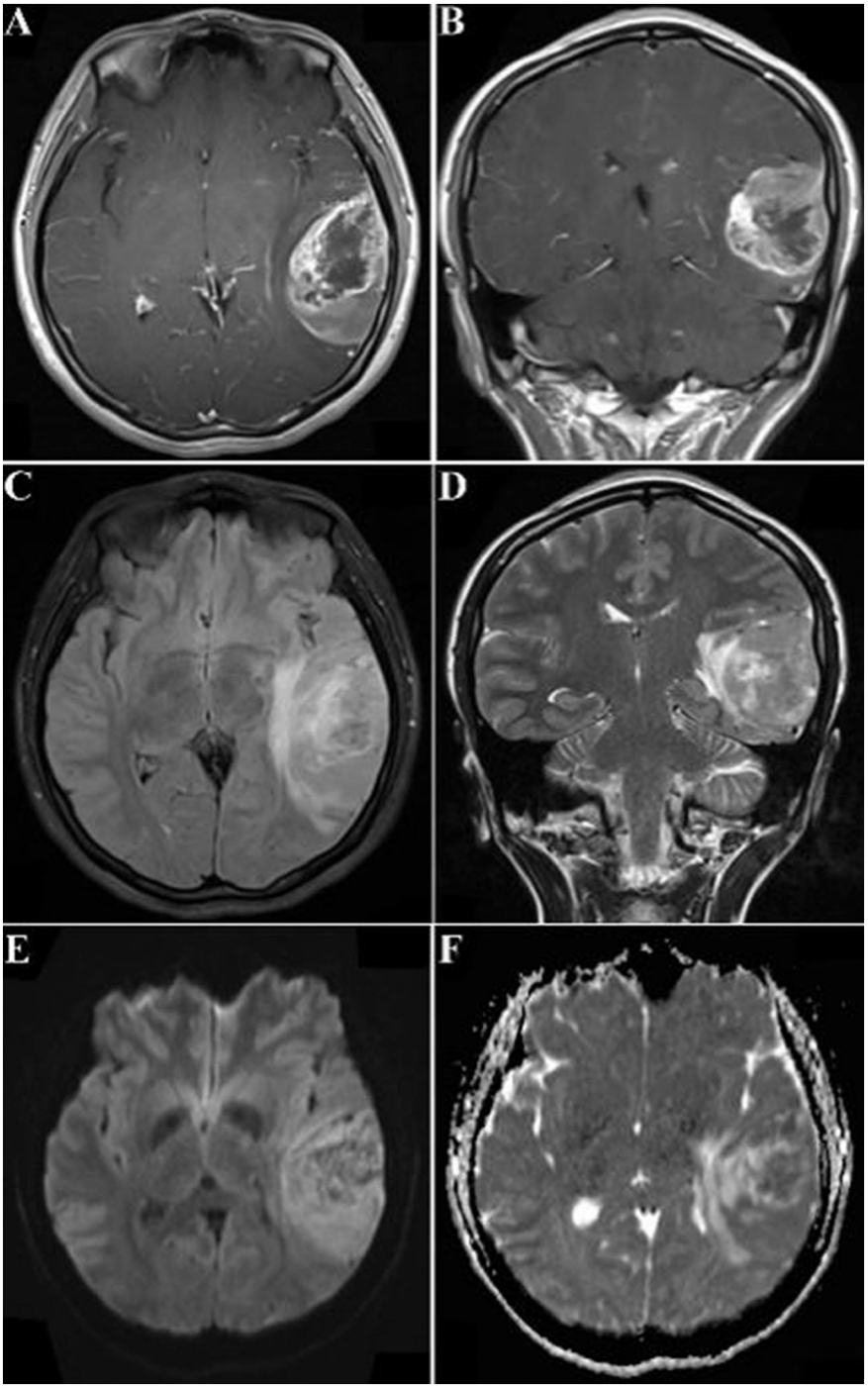

Fig. 1. (A) Axial T1-FLAIR-weighted image, (B) Coronal T1-FLAIR-weighted image,(C) Axial T2-FLAIR-weighted image,(D) Coronal T2-FLAIR-weighted image,(E) Axial diffusion-weighted image,(F) Axial apparent diffusion coefficient image. A left temporal lobe mass-type lesion is hyperintense on T2 and FLAIR images, hypointense on T1.The mass lesion is hyperintense on diffusion-weighted images, and the signal was further enhanced after enhanced scanning.

week were given. The second postoperative radiotherapy started in October 2018 using intensity-modulated radiotherapy; 6 MV-X rays were administered to the tumor bed area and residual tumor lesions after the second postoperative radiotherapy, (planning target volume 54 Gy/27 F, 2 Gy/F, 5 F/W), concurrently given with temozolomide (75 mg/m^2 qd × 42 d). During radiotherapy, bevacizumab 300 mg targeted therapy was given for one cycle to relieve the cerebral edema. In November 2018, a new brain MRI was captured and examined; compared with the MRI image before the second operation, the tumor recurrence in the anterior lower part of the left temporal occipital lobe was further enlarged. After the end of radiotherapy, 300 mg of bevacizumab + temozolomide (150 mg/m^2 for 5 consecutive days, 1 cycle every 28 days) combined therapy was given for one cycle, followed by 4 cycles of single-drug temozolomide chemotherapy according to the original plan. During radiotherapy and chemotherapy, the patient experienced grade I bone marrow suppression, mainly manifested as decreased white blood cells, accompanied by decreased appetite and fatigue. The quality of life (QOL) score was 55 points. A new head MRI taken and examined in January 2019 showed that the recurrence of the tumor was smaller than before, and its activity was lower as well. The patient's final chemotherapy treatment was administered in April of 2019. That month, another re-examination of the head with MRI confirmed that the condition was stable. In May 2019, the patient developed lumbosacral pain, QOL of 50 points. An MRI was administered (Fig. 3) to diagnose metastasis to the multiple lumbar vertebrae, appendages, and bilateral ilium. In June 2019, the patient received a total dose of 30 Gy in 10 fractions of radiotherapy for bone metastases in a local hospital, lumbosacral pain was less severe than before, QOL of 52 points. The patient was moved in July 2019 to our hospital, where three cycles of targeted combination chemotherapy of "bevacizumab 300 mg d 1 + irinotecan 160 mg d 2" were given, and the last treatment time was dated August 2019. During the treatment, a mass was found to be palpable on the sternum of the patient, which gradually increased in size and had a hard texture. In August 2019, a computed tomography (CT) scan was used to re-examine the region (Fig. 4); a soft tissue mass with sternal and T9, L1 vertebral body bone destruction was found. Then, a needle biopsy was performed for the local mass at the sternum. The pathological diagnosis was malignant tumor (biopsy specimen of sternal

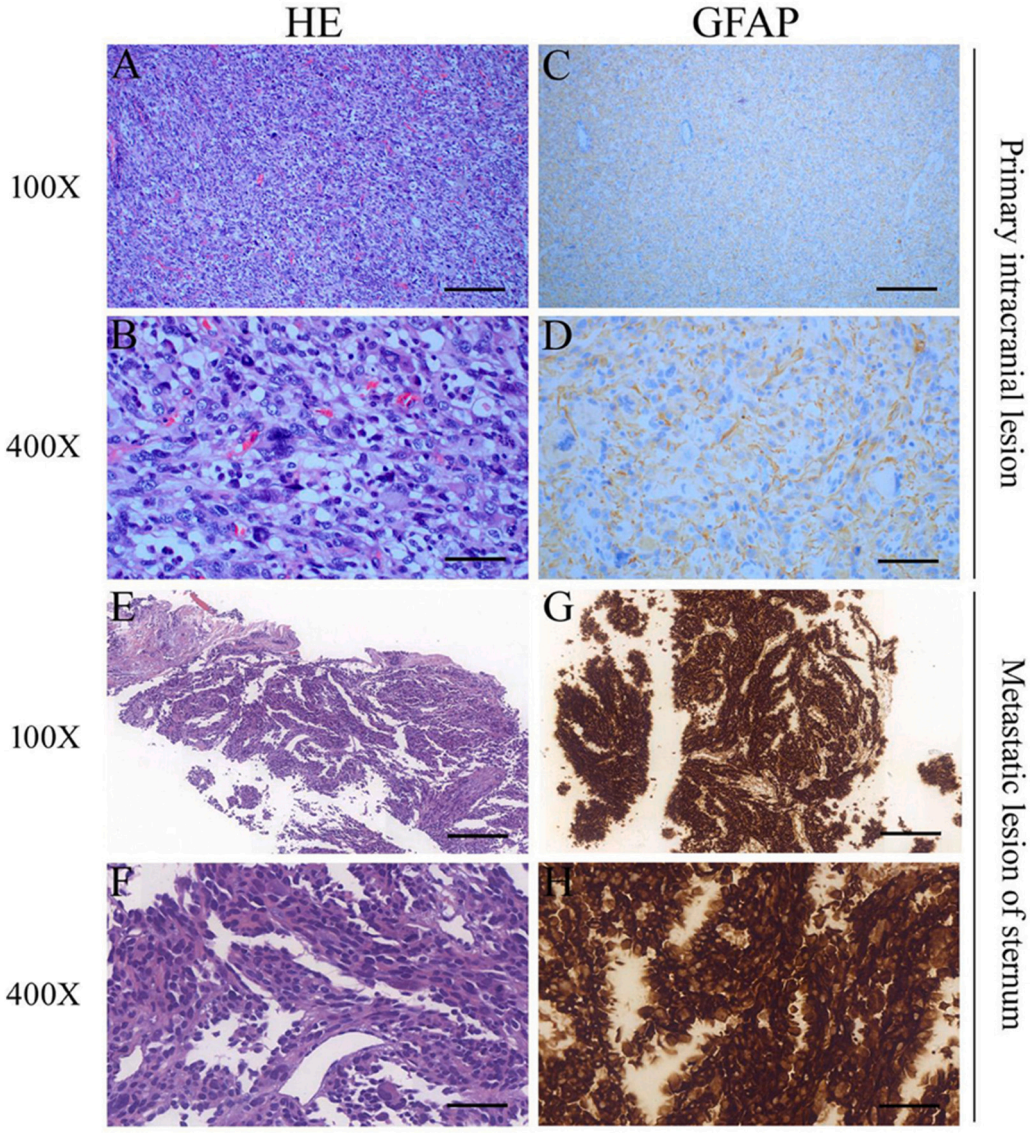

Fig. 2. (A) Hematoxylin and eosin (HE) staining of intracranial lesions (×100,bar = 200 μm), (B) HE staining of intracranial lesions (×400,bar = 50 μm), (C) Glial fibrillary acidic protein (GFAP) staining of intracranial lesions (×100,bar = 200 μm), (D) GFAP staining of intracranial lesions (×400,bar = 50 μm), (E) HE staining of sternal metastasis (×100,bar = 200 μm), (F) HE staining of sternal metastasis (×400,bar = 50 μm), (G) GFAP staining of sternal metastasis (×100,bar = 200 μm), (H) GFAP staining of sternal metastasis (×400,bar = 50 μm).

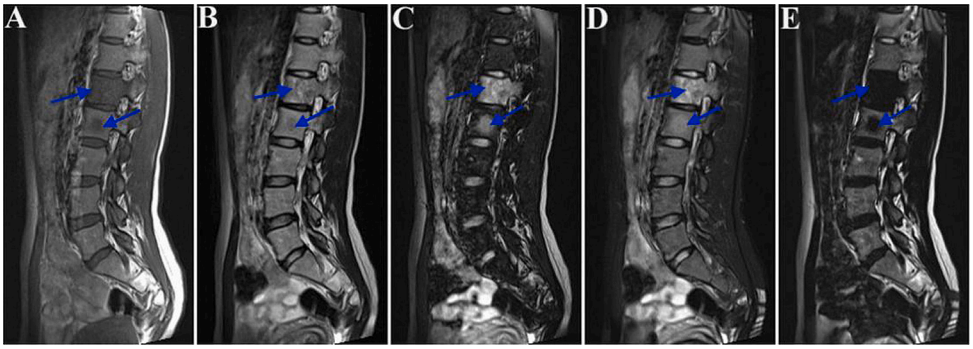

Fig. 3. (A) Sagittal T1-weighted image, (B) Dixon in phase T2-weighted image, (C) Dixon opposed phase T2-weighted image, (D) Dixon water T2-weighted image, (E) Dixon fat T2-weighted image. The metastatic lesions of the tumor are located in the first and second lumbar vertebrae, with low signal intensity on T1 weighted images and high signal intensity on T2 weighted images.

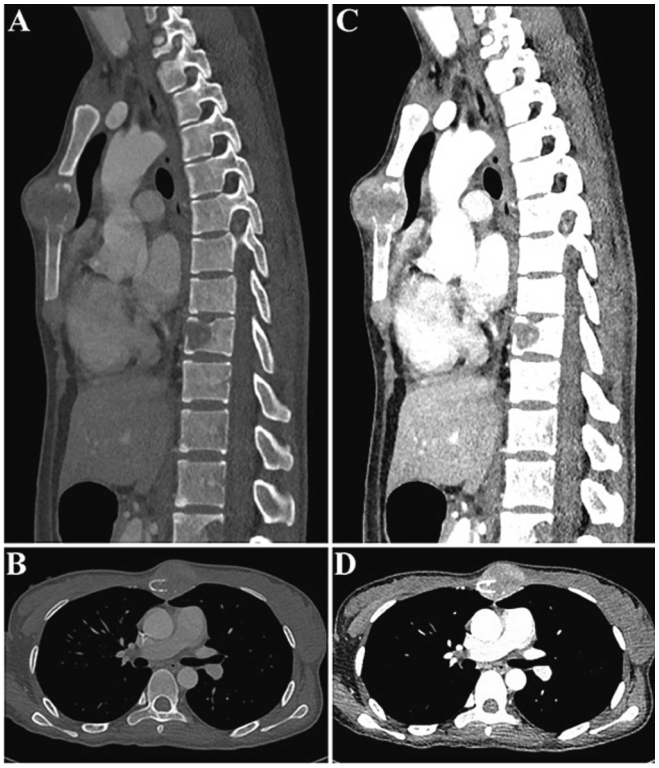

Fig. 4. (A) Sagittal plain CT image, (B) Axial plain CT image, (C) Sagittal enhanced CT image, (D) Axial enhanced CT image. The metastatic lesions of the tumor are located in the anterior chest wall, the 9th thoracic vertebra, and the 1st lumbar vertebra. The size of the metastatic lesions in the anterior chest wall is about 4.0 cm × 3.5 cm, accompanied by bone destruction of the sternum, and after enhanced scanning, the metastatic lesion was significantly enhanced.

soft tissue mass), and immunohistochemical examination (Fig. 2) confirmed that the diagnosis was consistent with the recurrence and metastasis of glioblastoma; the examination also identified several molecular features, such as GFAP expression. Anlotinib (12 mg qd × 14 days, with every 21 days considered to be a cycle) targeted therapy was started in September 2019. In October 2019, the patient complained of severe neck pain, simultaneously accompanied by anorexia, fatigue, poor mental state, frequent bed rest, QOL of 40 points. A CT scan was performed; osteolytic destruction was seen in the C6 vertebral body and its appendages, and a local soft tissue mass was found to have formed, suggesting metastasis. Palliative radiotherapy started in November 2019 with intensity-modulated radiotherapy; 6 MV X-rays were given to target the C6 metastatic lesions, and the planned 95 % isodose curve encompassed the patient's neck and shoulders (PTV 39 Gy/13 F, 3 Gy/F). The pain was less severe than before. During the radiotherapy, the patient experienced transient blindness in both eyes, simultaneously accompanied by grade II bone marrow suppression, mainly manifested as leukopenia and anemia, as well as occasional arrhythmias, so the radiotherapy was suspended and a total of 7 sessions were completed. The patient's neck pain had not been relieved, and her vision in both eyes had decreased. She often lied in bed, accompanied by fatigue and poor appetite, poor mental state, and loss of confidence in treatment. The QOL score was 28 points. A head MRI in November 2019 showed that, in addition to the original lesions, the left cerebellum and parietal lobes and both occipital lobes were all abnormally enlarged, which was attributed to an entirely new lesion. Later, the patient suffered from fatigue and poor appetite, with was accompanied by hypertension, arrhythmia, and electrolyte disturbance. In November 2019, she was given a cycle of “bevacizumab 300 mg” targeted therapy, and anlotinib was adjusted to 12 mg qod targeted therapy. In December 2019, the patient had obvious abdominal distension and underwent peritoneal puncture and catheter drainage. The exfoliated cells were checked and showed highly abnormal cells, which were considered to be possibly malignant. The general condition of the patient was poor, obvious body pain, fatigue, poor appetite, nausea and vomiting, abdominal distension, bedridden all day, indifferent expression, and loss of confidence in treatment, with a KPS score of 40 and QOL score of 24. Anlotinib was discontinued, and symptomatic and supportive treatment was given. She died at the end of December 2019.

3. Discussion

The latest cancer statistics report shows that there were approximately 310,000 new cases and 250,000 deaths of brain and nervous system tumors worldwide in 2020 [3]. GBM is the most common primary malignant brain tumors in adults. It accounts for >60 % of primary brain tumors. ECM is a rare phenomenon of GBM. To our best knowledge, most cases of extracranial metastasis of glioma have been reported in the form of cases and the number is very small. According to reports, the blood–brain barrier; the thickening of the vascular basement membrane and dura mater; and the lack of extracellular matrix synergistically prevent the spread of GBM blood and lymphatic channels [4,5]. Mourad et al. [6] transplanted delayed brain tumor (DBT) cells into the brains and bodies of three rodent models to observe the relationship between tumor growth and immunogenicity differences; the results confirmed that the barriers prevent timely growth due to the rarity of ECM in GBM. In addition, due to the highly malignant and invasive nature of GBM, most patients died within 20 months after diagnosis, as there was insufficient time for the occurrence or detection of distant metastasis [4].

Although rare, the ECM of GBM has been well documented. In 1928,

L. Davis [7] was the first to report a case of ECM of cerebral cavernous blastoma. The patient underwent surgery and deep X-ray therapy. The final autopsy report confirmed the intracranial recurrence of cavernous blastoma with lung metastasis, and L. Davis believed that hematogenous metastasis was the ECM route cause. Over time, more and more cases were reported. Lun et al. collected and analyzed 83 ECM cases from GBM, published between 1928 and 2009 [8], and their analysis estimated that the median time from metastasis to death was only 1.5 months. However, the survival time increased progressively with each decade from 1940 to 2000, which they attribute to the use of MRI. J. Undabeitia [9] also believes that the increase in the incidence of ECM is related to the improvement of medical treatment as a whole. Epidemiologically, younger, healthier patients appear to be more prone to extracranial metastases, most likely because of longer overall survival (OS) compared with older GBM patients with multiple chronic diseases [10].

Thus far, the ECM-related mechanism of GBM has not been identified, although additional mechanisms have been proposed gradually. It has been reported that most ECMs spread to the spinal cord (through the pia mater or intramedullary) or occur after the above barrier is destroyed (e.g., through craniotomy or intraventricular shunt, in which GBM achieves blood transfer) [1,11,12]. Anghileri et al. [13] identified circulating tumor cells (CTCs) from the peripheral blood of 29 GBM patients, thus confirming that GBM hematogenous spread is an intrinsic biological characteristic. The patient we reported discovered multiple bone metastases in the 10th month after two craniotomy surgeries, followed by highly suspicious abdominal metastases. We also believe that the two surgeries disrupted the blood-brain barrier and malignant tumor cells achieved blood metastasis, spreading to the bones and abdominal cavity. The patient had a clear consciousness in the end stage and no obvious intracranial progression such as hemiplegia. However, the patient experienced significant systemic pain due to extensive bone metastasis, and a large amount of ascites was produced due to highly suspected abdominal metastasis, accompanied by fatigue, poor appetite, nausea and vomiting, significant hypoproteinemia, electrolyte disorders, arrhythmia, ultimately leading to cachexia. Therefore, we believe that extensive extracranial metastasis is the main cause of patient death. Although most ECM of GBM occurred after neurosurgery, S. Hulbanni [14] reported a case of preoperative ECM in 1976. The patient had a right lung mass on the preoperative X-ray film. The autopsy confirmed lung, bronchial lymph node, and lumbar spine metastases. They believed that GBM invaded the vascular cavity, and were suspicious that cell embolism to the lung was the mode of transmission. In addition, epidemiological data have shown that surgical patients have a longer OS, which may provide more time for metastases, as shown by the simultaneous occurrence of surgical resection and GBM metastasis [15]. Therefore, neurosurgery cannot simply be considered as a sole trigger for metastasis.

A study by Park et al. [16] suggested that the emergence of tumor subclones may be associated with metastasis in GBM. They focused on evaluating common genetic alterations in the DNA of six primary and metastatic GBM; notable findings include TP53 mutation, CDKN2A/p16 loss, EGFR amplification, and allelic loss of chromosomes 1p, 10q, and 19q. Different TP53 alterations were found in two primary and metastatic lesions. This finding suggests that some metastatic lesions may be characterized by TP53 mutations and represent the emergence of subclones that are not necessarily predominant in the primary tumor. Onda et al. [17] conducted a histological study with 14 patients with gliomas with cerebrospinal fluid dissemination. Patients with GFAP-negative tumors were found to be more prone to cerebrospinal fluid invasion, while GFAP-positive tumor cells showed high invasion at the primary site. They believe that the expression of GFAP may be a histological sign of spinal cord spread. Additional evidence shows the existence of the brain lymphatic system; dissemination through the lymphatic system is also considered a route of tumor spread [18].

The standard treatment for intracranial GBM remains maximal surgical resection, followed by postoperative adjuvant radiotherapy or concurrent chemoradiotherapy [1]. Still, overall efficacy is still unsatisfactory. In recent years, electric field therapy has been proposed to have a certain curative effect in GBM. Several reports pointed out [19] that standard concurrent radiotherapy and chemotherapy after surgery, combined with electric field therapy during maintenance chemotherapy, may synergistically reduce brain tumors. Stupp et al. [20] divided 695 GBM patients who had received standard radiotherapy and chemotherapy into two groups, namely, electric field combined with temozolomide and temozolomide alone. The results showed that the combined treatment could significantly improve both the progression-free and the overall survival rates, further confirming the positive role of electric field treatment in GBM. Given that electric field therapy is safe and effective, it is used for the treatment of new GBM (level 1 evidence) and recurrent high-grade GBM (level 2 evidence) diagnoses [19,21]. At present, various research centers are working to advance the interventional timing of electric field therapy. These researchers are attempting to combine electric field therapy in the postoperative synchronous radiotherapy and chemotherapy stage to further improve the progression-free survival rate and overall survival rate of patients. However, the current price of electric field treatment is still relatively expensive, limiting its overall reach.

Still, the optimal treatment for metastatic GBM has not yet been identified. In metastatic GBM, lung metastasis is the most severe prognostic factor [8]. Current reports suggest that the treatment of metastatic GBM should focus on systemic chemotherapy [4,8], although the optimal chemotherapy drug routine has not been identified. The most common treatments include temozolomide and nitrosourea drugs [1,22]. Bevacizumab, a vascular endothelial growth factor inhibitor, has achieved high efficacy and tolerability in several studies, either as monotherapy or with chemotherapy [23,24]. Still, for newly diagnosed cases of GBM, the addition of bevacizumab to standard treatment does not improve the overall survival rate, and it is associated with the high incidence of early adverse events such as hypertension and thromboembolism. Therefore, the prescription of bevacizumab in newly diagnosed cases of GBM is not recommended [25]. In addition, although the immune checkpoint inhibitor therapy that has emerged in recent years has significantly improved the overall survival of several advanced tumors (e.g., melanoma, lymphoma, lung cancer, and kidney cancer), no obvious effects were evident in newly diagnosed cases of GBM and recurrent GBM [26] . Laperiere N et al. [27] believed that anlotinib had a “sensitization” effect on the radiotherapy of glioma. Although our patient, who was treated with anlotinib, experienced this effect in the short term, there was no obvious evidence-based medical evidence for its role in recurrent glioma. In addition, the condition of these patients is severe and their quality of life is low. In addition to medication treatment, we should also pay attention to psychological, nutritional, exercise, and pain care, and even plan nursing activities to minimize interference with their sleep, minimize the psychological burden on patients, enhance treatment confidence, and improve quality of life.

4. Conclusion

We reported a rare case of extracranial metastasis of GBM, which was treated with a combination of radiotherapy, chemotherapy, and targeted therapy, reducing pain and prolonging survival. We believe that the patient's extracranial metastases may have occurred through blood. Young “long-term survivors” who have undergone surgery seem to have a higher risk of extracranial metastasis. Timely detection and early treatment can improve the overall quality of life of the patient.

Ethical approval

Ethical approval for this retrospective study was provided by the Ethical Committee of Nantong Tumor Hospital, Nantong, China on 8 August 2022 (No. 2022-059-1).

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Author contribution

Pei Gu: concept, consent, literature review, drafting of the initial and final manuscript, approval of the final manuscript.

Xiaochun Xia: concept, consent, drafting of the final manuscript, and approval of the final manuscript.

Yongsheng Ding, Guihua Zheng: image processing.

Pengqin Xu: supervision.

Guarantor

The Guarantor is: Pengqin Xu.

Research registration number

Not applicable.

Consent

Written informed consent was obtained from the parents for the publication of this case report and accompanying images.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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