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Gliosarcoma with Systemic Metastasis Showing Favorable Response to Ifosfamide, Carboplatin, and Etoposide Chemotherapy: An Autopsy Case Report

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Abstract

Gliosarcoma is a rare malignant neoplasm. It accounts for approximately 2% of all glioblastomas. To date, there is no established treatment method for gliosarcoma, and a variety of therapies, such as surgical resection, radiotherapy, and chemotherapy, are typically employed. Here, we describe a patient with gliosarcoma who, despite multiple tumor metastases throughout the body, including the lungs and lymph nodes, achieved a relatively long survival due to salvage therapy with local irradiation and remarkably effective chemotherapy with low-dose ifosfamide, carboplatin, and etoposide therapy. When the patient died, we performed autopsy and confirmed the nature of the primary and metastatic tumor cells that had spread throughout the patient's body. Clinical and systemic histological studies also suggested the possibility of re-metastasis to the brain from systemic metastatic foci. Gliosarcoma appears to have characteristics similar to sarcoma as well as a higher risk of systemic metastasis. Therefore, a careful follow-up is necessary in such patients.

Keywords: ICE chemotherapy, extracranial metastasis, gliosarcoma

Introduction

Gliosarcoma (GS) is a rare variant of glioblastoma that accounts for approximately 2% of all glioblastomas. It has a biphasic histological composition with both gliomatous and sarcomatous elements.[1,2] Furthermore, it has a higher propensity for extracranial metastasis than glioblastoma, and several reports have demonstrated extracranial metastases to numerous sites, with the lungs, liver, and lymph nodes being the most common.[2] Currently, the prognosis of GS is worse when extracranial metastasis is present. Although therapy with temozolomide (TMZ)-based chemoradiotherapy is widely employed because GS is thought to be a variant of glioblastoma, evidence of its effectiveness remains limited.[3,4] Other chemotherapeutic agents, such as CCNU, bevacizumab, carboplatin, tamoxifen, and thalidomide, have been tested;[5,6] however, its clinical effectiveness has not been determined. Herein, we present a case of GS in which chemotherapy was effective for extracranial metastasis following standard treatment with the Stupp regimen.

Case Report

A 59-year-old man was transported from his workplace to the hospital by ambulance due to a generalized tonic-clonic seizure. Magnetic resonance imaging (MRI) of the head revealed a mass lesion in the left temporal lobe with a ring-shaped contrast effect (Fig. 1A). Gross total resection was performed. The postoperative diagnosis was GS

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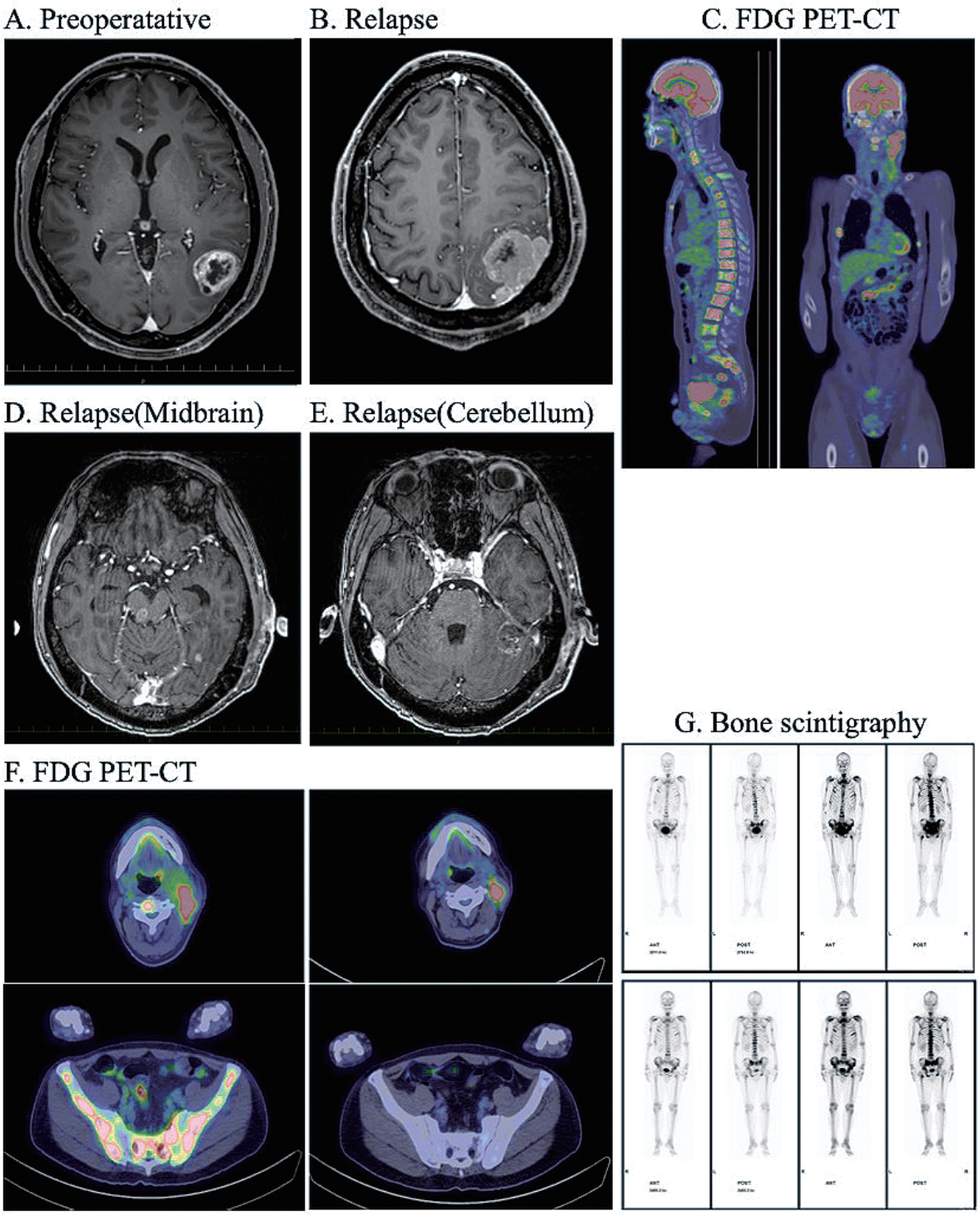

Fig. 1 Radiological findings. (*A*) Magnetic resonance imaging (MRI) images taken before the first craniotomy. (*B*) MRI images taken after the second craniotomy. (*C*) Positron emission tomography-computed tomography (PET-CT) before systemic chemotherapy. (*D, E*) Contrast-enhanced MRI of the head during intracranial re-metastasis. (*F*) Comparison of PET-CT. The two images on the left were taken before the ICE therapy, whereas the two images on the right were taken after five courses of the ICE therapy. (*G*) Comparison of bone scintigraphy. The top image was taken before the ICE therapy, whereas the bottom image was taken after five courses of the ICE therapy.

(isocitrate dehydrogenase 1/2 wild type and O^6-methylguanine-DNA-methyltransferase [*MGMT*] unmethylated). Concurrent chemoradiotherapy with local irradiation (60 Gy/30 Fr) and temozolomide (75 mg/m^2), followed by

maintenance of temozolomide (5 days on/23 days off), was prescribed.

Approximately 6 months after the initial operation, a local recurrent lesion, extramedullary in location, was detected in the left parietal region (Fig. 1B). Consequently, craniotomy and local radiotherapy (Novalis: peripheral dose of 50 Gy) were performed. Subsequently, local recurrence occurred twice more, and local radiotherapy was performed three times in total for these lesions.

About 6 months after the second surgery, positron emission tomography-computed tomography and bone scintigraphy revealed multiple metastases to the cervical lymph node and spine as well as multiple bone metastases (Fig. 1C). Biopsy of the cervical lymph nodes confirmed GS metastasis. Because the tumor was thought to be resistant to temozolomide already, we decided to administer chemotherapy using IFOS/CBDCA/VP-16 (low-dose ICE therapy) with slight modifications to the previously reported regimen. Both carboplatin and etoposide were administered at a dose of 100 mg/m^2/day for 3 days, whereas ifosfamide was administered at 1500 mg/m^2/day for 3 days. This regimen was repeated every 4 weeks.[7]

The chemotherapy was surprisingly effective, and remarkable shrinkage of the metastatic lesions was observed (Fig. 1F, G). Over the next year, the patient was treated with 11 courses of low-dose ICE chemotherapy. Although metastatic lesions increased during the chemotherapy interval, tumor size reduction was achieved after each course of low-dose ICE chemotherapy.

At 62 years of age, 13 months after the ICE chemotherapy initiation, the patient presented with weakness and sensory disturbances in both the lower limbs. MRI revealed enlargement of the metastatic lesions in the right upper extremity, sacrum, thoracic spine, and cerebrum. Thus, stereotactic radiotherapy was performed (Supplementary Fig.). Novel metastatic lesions were also detected in the cerebellum and midbrain. Because ICE chemotherapy was no longer effective, procarbazine/ACNU/vincristine was administered; however, the lesion further progressed (Fig. 1D, E) and was subsequently treated with local radiation therapy.

After readmission to our hospital, metastases to both shoulders were discovered, and irradiation of the shoulders, cerebellum, and middle brain was performed. During the course of the treatment, the patient's respiratory condition dramatically deteriorated, and he died 30 months after the initial diagnosis.

Pathological findings

The first postoperative pathological finding indicated growing atypical glial cells with a high nuclear-cytoplasmic ratio and increased chromatin content in large and small foci (Fig. 2A). Sarcomatoid tumor components with pleomorphic features were observed between foci, indicating differentiation into cartilage and bone. As presented in Fig. 2B, the Ki-67 labeling index was high (>90%) in the tumor cells, ATRX staining was positive, glial fibrillary acidic protein (GFAP) staining was partially positive, MGMT staining was positive, and mutant isocitrate dehydrogenase1 (*IDH1* R132H) was non-existent. Specimens obtained by cervical lymph node biopsy and reoperation showed similar findings (data not shown).

Autopsy was performed (Fig. 3A-E). As gross findings of the body surface, many hard skin nodules (1-4 cm in diameter) were observed in the head and left shoulder areas. Hard, whitish nodules were also found on the left and right lung surfaces and thoracic cavities. The amounts of blood pleural effusion were 2000 and 1100 mL on the left and right sides, respectively. Hard, whitish nodules were also detected in the fat around the heart surface and in the left kidney, pancreas, left cerebellum, right midbrain, and left temporal lobe. Histological analysis revealed that all hard nodules were GS with cartilage formation, and the histological features were similar to those of the primary lesion. Multiple micrometastases were detected in the liver and bone marrow. Aspiration pneumonia and diffuse alveolar damage were observed in the lungs.

Discussion

GS has been reported to be more prone to extracranial metastasis than glioblastoma (11% vs. 0.2%-4.0%, respectively).[2,8] Therefore, a careful systemic follow-up might be necessary, even when intracranial lesions are under control.

In the autopsy, tumor lesions were found in the cerebrum (left temporal lobe to occipital lobe), left cerebellum, midbrain, bilateral lungs, liver, pancreas, bone marrow, pericardial lipid tissue, subcutaneous tissue, left kidney, and lymph nodes (hilar and para-aortic). Sarcoma-like components were clearly visible in all lesions, including the primary site, and GFAP-staining was considered to be only partially positive, with fewer glioma-like components. A previous report demonstrated that tumors with increased sarcoma components are more prone to metastasis;[9] thus, we considered that multiple metastases to the whole body of patients, such as our case, might be explained by the higher proportion of sarcoma components.

A previous meta-analysis revealed that the median overall survival of GS patients from the time of the initial diagnosis was 13 ± 2.4 months, whereas the median overall survival from the time of the diagnosis of metastases was 6.0 ± 0.8 months.[8] Compared to previous reports, our patient had a longer survival of approximately 30 months from the initial diagnosis and 18 months from the metastatic diagnosis.

Among the various factors that may lead to longer survival, the effectiveness of low-dose ICE chemotherapy for metastatic lesions may have made a significant contribution to prolonged survival. ICE chemotherapy is generally

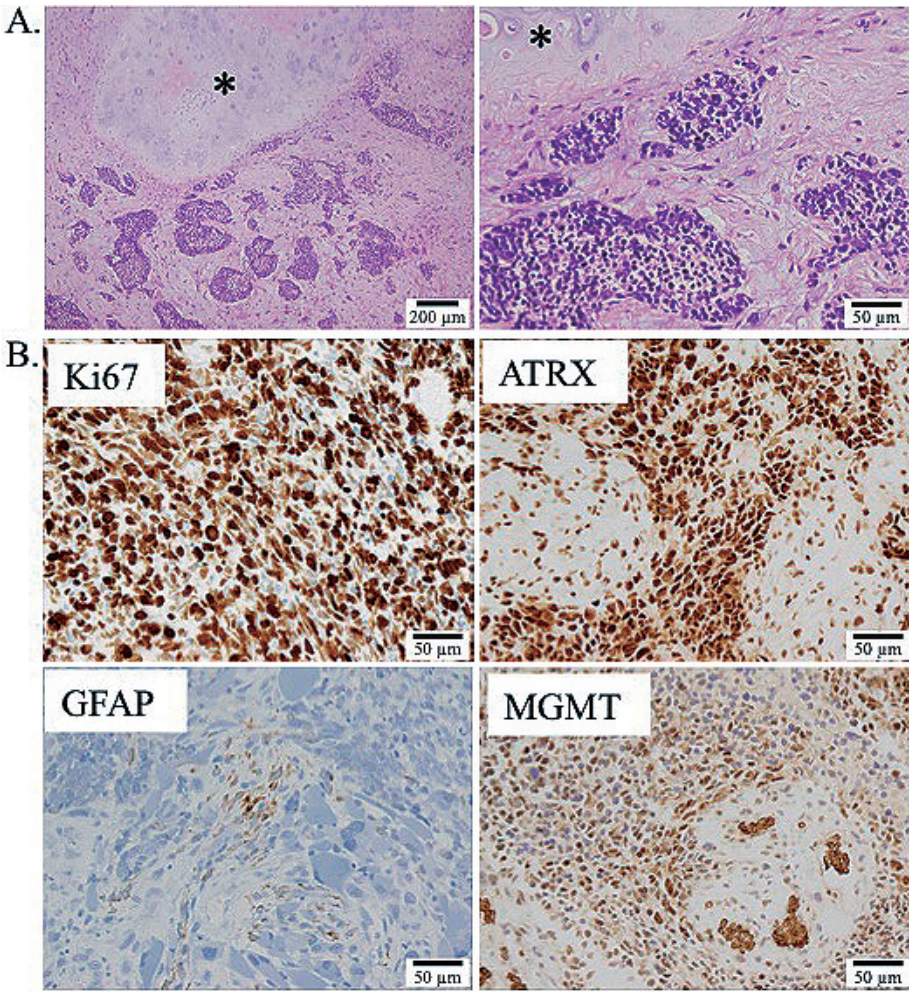

Fig. 2 Microscopic findings of the surgically resected sample from the first surgery. (*A*) Hematoxylin and eosin staining showed tumor cells with undifferentiated morphological features. The cells formed differently sized foci with cartilaginous metaplasia (*). Scale bars: 200 μm (left) and 50 μm (right). (*B*) Immunohistochemistry for Ki-67, ATRX, GFAP, and MGMT. Scale bar: 50 μm.

used for soft tissue sarcomas, and due to hematologic toxicity, the adult dose is reduced from the pediatric dose.[10] Although the effectiveness of ICE chemotherapy has not been reported in recurrent GS, our case showed a marked reduction in the size of the cervical lymph node lesions following chemotherapy. Furthermore, GFAP was partially positive in both the primary and metastatic lesions, suggesting a high content of sarcoma components in our case. Such histological characteristics might be the reason for the unexpected effectiveness of ICE chemotherapy. In fact, there have been reports demonstrating a relatively long-term survival in cases where carboplatin was used for GS with a high sarcoma component.[5]

Molecular-targeted therapy is currently one of the treatment options to be considered for carcinomas; however, we could not perform cancer multigene panel testing for this case. Previous studies have reported that *BRAF*, *EGFR*, *CDKN2A*, *NF1*, and *PTEN* are frequently altered genes in GS and might be potential therapeutic targets.[11]

We hypothesized that the tumor in this patient had once metastasized extracranially and that these tumor cells from the extracranial metastatic lesion subsequently metastasized intracranially due to the following reasons: 1) the cerebellar and midbrain metastatic lesions were located distant from the primary site, and these intracranial metastases developed more than 1 year after the disappearance of intracranial tumors; 2) the autopsy findings indicated that the later recurrent brain lesions, especially in the midbrain, had relatively clear boundaries with the surrounding area and were non-contiguous with the primary lesion. However, the origin of intracranial metastasis is not conclusive. In fact, brain metastasis of sarcoma, which is known to be a poor prognostic factor,[12] is rare, and there has been no previous report of GS that metastasized to the brain after systemic metastasis.

Further molecular analysis of the primary tumor and metastases is expected to elucidate the mechanism of disease progression, origin of metastatic lesions, and favorable

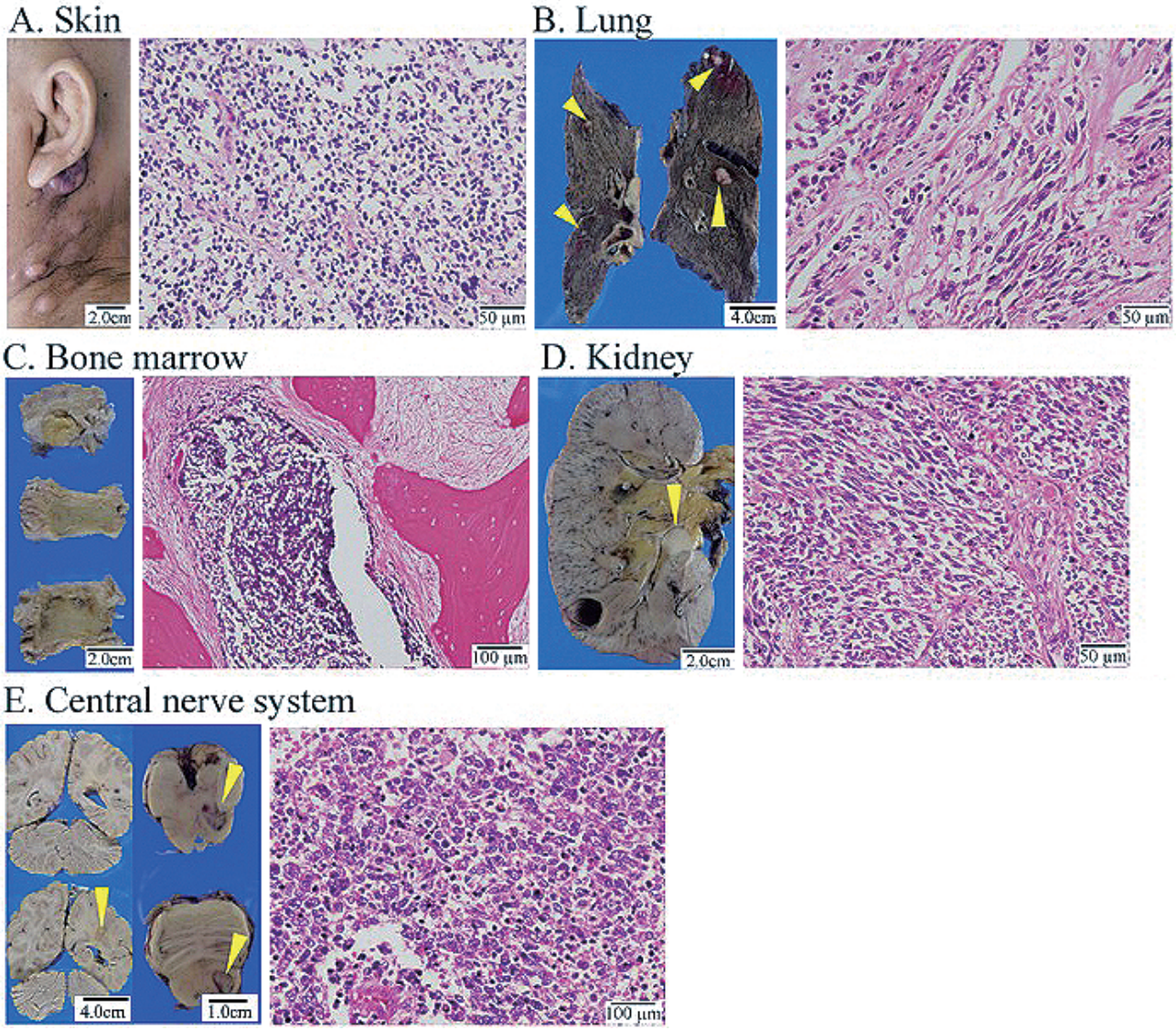

Fig. 3 Pathological findings from the post-mortem autopsy. Hard, whitish nodules were detected in the (*A*) the skin around the neck and ears, (*B*) lungs, (*D*) left kidney, and (*E*) left temporal lobe and right midbrain. Ossification was observed in the (*C*) bone marrow. Tumor cells had proliferated and formed solid foci, and the cartilage was sporadically detected. The trabeculae were enlarged, and fibrosis was detected in the bone marrow. Scale bar: 50 μm.

response to chemotherapy in this case in the future.

In summary, we have presented a case of GS with multiple extracranial metastases. GS appears to share characteristics of sarcoma and pose a higher risk of systemic metastasis. Thus, a careful follow-up is necessary in such patients. Our experience with this case demonstrated that low-dose ICE chemotherapy may be effective for GS and particularly for cases with an abundant sarcomatous component.

Supplementary Material

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Informed Consent

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

Conflicts of Interest Disclosure

The authors declare no conflicts of interest associated

with this article.

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