Diagnosis and Treatment of Early-Stage Glioblastoma

Abstract

Early-stage glioblastoma has few identifiable findings; clinical significance of its early diagnosis and treatment remains unclear as no report has described treatment and long-term follow-up for early-stage glioblastoma. Here, we report a case of a 69-year-old woman with early-stage glioblastoma treated by microsurgical resection and chemoradiotherapy. Magnetic resonance imaging (MRI) revealed a small high-intensity lesion in the right temporal lobe on T2-weighted imaging. Contrast-enhanced T1-weighted MRI revealed ring enhancement. On magnetic resonance spectroscopy, the lesion demonstrated increased choline and reduced N-acetyl-aspartate levels compared with the normal brain. Positron emission tomography with ^{11}C-methionine (MET) revealed ^{11}C-methionine uptake in the lesion. Microsurgical resection was performed, and glioblastoma was pathologically diagnosed. The patient was treated with local radiotherapy and temozolomide chemotherapy postoperatively. Eight years postoperatively, the patient is surviving without tumor recurrence, but progressive cognitive impairment developed 6 years' postoperatively. Aggressive treatment of early-stage glioblastoma may improve its extremely poor prognosis. Conversely, cognitive impairment may become a significant medical and social problem when effective therapies for glioblastoma are developed.

Keywords: *Cognitive impairment, early diagnosis, early stage, early treatment, glioblastoma, long-term survival*

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Introduction

One reason for the poor outcome of glioblastoma may be delayed diagnosis and treatment; however, knowledge about the early stage of glioblastoma is limited. Although small glioblastomas (with diameters of 8–14 mm) have been described as early- or initial-stage glioblastomas by several authors.[1-3] These were pathologically diagnosed and treated after tumor progression, not at an early stage. Here, we report the case of a glioblastoma that was diagnosed and surgically treated at an early stage. To the best of our knowledge, this is the first case report of a long-term follow-up of glioblastoma treated at an early stage.

Case Report

A 69-year-old Japanese woman presented with transient finger tremor. No abnormalities were detected in the neurological and general examinations, but T2-weighted images (T2WI) and fluid-attenuated inversion recovery magnetic resonance imaging (MRI) revealed a 12 × 10-mm hyperintense lesion in the right hippocampal body [Figure 1a], which was hypointense on T1-weighted images (T1WI) [Figure 1b] and diffusion-weighted imaging [Figure 1c]. Contrast-enhanced T1WI images demonstrated lesion ring enhancement [Figure 1d and e].

Single-voxel magnetic resonance spectroscopy of the lesion revealed increased choline and decreased N-acetyl aspartate levels without high levels of lactate or lipids. ^{11}C-methionine (MET) positron emission tomography (PET) showed increased MET uptake in the lesion [Figure 1f], with a maximum standardized uptake value of 1.73 and tumor/normal brain ratio of 1.45. No abnormal uptake was observed on whole body ^{18}F-fluorodeoxyglucose PET. The diagnosis was that the lesion was likely to be a malignant glioma.

Gross total lesion removal was performed using the transcortical (middle temporal gyrus)–transventricular approach, guided by surgical navigation and the visual evoked potential. The lesion was a grayish, soft, and comparatively

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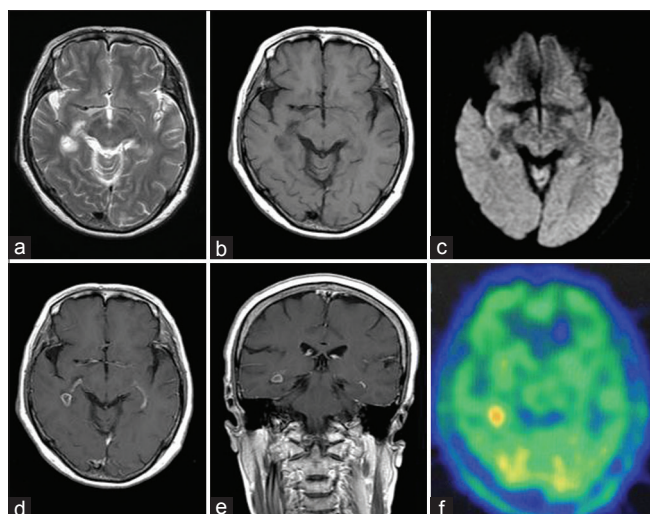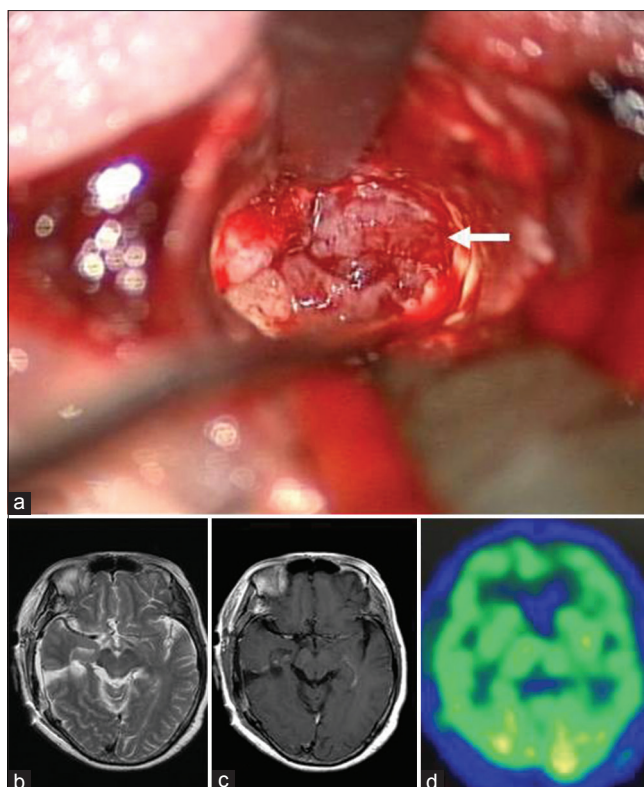Figure 1: Preoperative magnetic resonance imaging and ¹¹C-methionine positron emission tomography. These studies demonstrated a 12 mm × 10 mm lesion in the right hippocampal body, showing hyperintense on T2-weighted magnetic resonance imaging (a) and hypointense on T1-weighted magnetic resonance imaging (b) and diffusion-weighted images (c). T1-weighted gadolinium-enhanced magnetic resonance imaging showed lesion ring enhancement (d: axial view; e: coronal view). ¹¹C-methionine positron emission tomography image showing an area of ¹¹C-methionine accumulation in the right temporal lesion (f)

well-demarcated tissue, making it relatively easy to discriminate from the surrounding normal brain tissue [Figure 2a]. A rapid intraoperative pathological diagnosis indicated that the lesion was a glioblastoma and no tumor cells were detected in the brain tissue surrounding the tumor. We, therefore, chose resection of the tumor alone rather than an extensive resection.

In a pathological analysis, hematoxylin and eosin staining demonstrated extensive necrotic tissue surrounded by tumor cells [Figure 3a]. High-magnification microscopy revealed pleomorphic tumor cells with nuclear atypia [Figure 3b] and microvascular proliferation [Figure 3c]. Immunohistochemical staining was positive for glial fibrillary acidic protein [Figure 3d] and epidermal growth factor receptor [Figure 3e], and negative for isocitrate dehydrogenase (IDH) 1 R132H [Figure 3f] and p-53. These histopathological findings were consistent with features of glioblastoma. The MIB-1 proliferation index was 3%–5%.

Genetic analysis demonstrated the wild-type status of the IDH 1 and 2 genes and TERT promoter, as well as the absence of O⁶-methylguanine-DNA methyltransferase (MGMT) methylation and 1p19q codeletion. The final diagnosis was glioblastoma IDH-wild type.

Postoperatively, the patient exhibited no neurological deficit, and no residual tumor was observed on MRI [Figure 2b and c] and MET-PET [Figure 2d]. The patient underwent focal radiation therapy (a total of 60 Gy over 30 days) and concomitant temozolomide (TMZ) chemotherapy (75 mg/m^2/day), followed by six maintenance TMZ chemotherapy courses (150 mg/m^2 for 5/28 days).


Figure 2: Intraoperative findings and postoperative studies. The lesion had grayish, soft, and relatively well-demarcated tissue (arrow) (a). Total lesion removal was confirmed on postoperative magnetic resonance imaging (b); T2-weighted magnetic resonance imaging (c); T1-weighted gadolinium-enhanced magnetic resonance imaging; and on ¹¹C-methionine positron emission tomography (d)

No tumor recurrence has been observed on follow-up MRI for 8 years' postoperatively. However, the patient began suffering from memory disturbance 6 years' postoperatively, at the age of 75 years. Her standard profile score on the Rivermead Behavioural Memory Test was 15/24, which was lower than the cutoff point for her age. Currently, the patient lives in a nursing home for the elderly because of her progressive memory disturbance.

Discussion

One reason for the poor outcomes experienced by patients with glioblastoma may be delayed diagnosis and treatment, but there are currently no standard diagnostic or therapeutic strategies for early-stage glioblastoma. Ideguchi *et al.* summarized the clinical characters of all previously reported early-stage glioblastoma cases (15 cases). They reported that the MRI findings of early-stage glioblastoma were a small, ill-defined, hyperintense lesion on T2WI, and subtle or no contrast enhancement on contrast-enhanced T1WI; thus, it was difficult to distinguish from nonneoplastic diseases, including ischemic and demyelinating diseases.[2] In our patient, ring enhancement on contrast-enhanced T1WI was characteristic of glioblastoma. In addition, increased choline and decreased *N*-acetyl aspartate levels on magnetic resonance spectroscopy and obvious MET uptake on
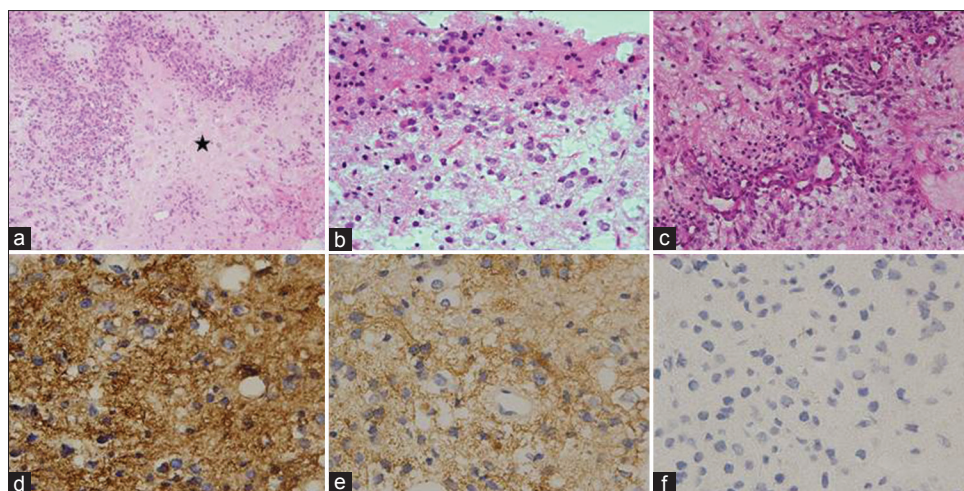
Figure 3: Pathological findings. Hematoxylin and eosin staining demonstrated a large necrotic area (star) surrounded by tumor cells (a), pleomorphic tumor cells with nuclear atypia (b), and microvascular proliferation (c). Immunohistochemical analyses demonstrated positive staining for glial fibrillary acidic protein (d) and epidermal growth factor receptor (e) and negative staining for isocitrate dehydrogenase 1 R132H mutation-specific antibody (f). Original magnifications: ×40 (a), ×200 (c), ×400 (b and d-f)

MET-PET were useful indicators that the lesion was neither ischemic nor demyelinating disease but a neoplastic disease such as glioblastoma.

Early-stage glioblastomas can develop into bulky mass lesions within a few weeks, with dismal prognosis.[1,2] We therefore performed early-stage lesion treatment instead of careful MRI follow-up.

The 5-year survival of glioblastoma patients with unmethylated MGMT promoter has been reported to be 8.3%,[4] and the 10-year survival in glioblastoma has been estimated as 0.71%.[5] The 8-year recurrence-free survival of our patient is therefore a rare phenomenon. According to the established prognostic factors for glioblastoma,[6] our patient's age of 69 years and unmethylated MGMT promoter were negative factors, whereas her high Karnofsky Performance Status and the gross total resection (>98%) were positive factors. The early treatment may also have contributed to these positive factors, improving her survival. In addition, the patient's MIB-1 proliferation index of 3%–5% was low compared with that of other patients with glioblastoma, and this may have been related to her long-term survival. However, MIB-1 index values in glioblastoma vary widely (0%–76.4%), and an association with clinical outcome has not been demonstrated.[7] Although developed glioblastoma is generally an infiltrative tumor, the extent of the peripheral infiltrating margin shows great variability.[8] The low invasive character of the tumor in the present case, demonstrated by the intraoperative findings and pathological diagnosis, may be another factor in the patient's long-term survival.

It is unclear whether the low proliferation index and the low invasiveness of this tumor were because of the tumor stage or the biological nature of this specific tumor because there is little information available about early-stage glioblastoma. Further clinical and biological research on early-stage glioblastoma is necessary.

Deterioration in mental status during adjuvant TMZ chemotherapy following concomitant chemoradiotherapy has been reported to affect 56% of elderly patients.[9] Postoperative radiotherapy may therefore have been the cause of the cognitive dysfunction in our patient.

Identifying early-stage glioblastomas remains difficult. However, the development of technologies such as liquid biopsy[10] and the detection of serum biomarker[11] may enable early diagnosis and early treatment of glioblastoma in the future and may improve the prognosis of glioblastoma. On the other hand, cognitive impairment resulting from treatment may become a significant medical and social problem.

Conclusion

Opportunities to diagnose and treat early-stage glioblastomas will increase with the development of technologies. However, we have insufficient knowledge of early stage glioblastoma. Further biological and clinical studies on early-stage glioblastoma are required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Faguer R, Tanguy JY, Rousseau A, Clavreul A, Menei P. Early presentation of primary glioblastoma. Neurochirurgie 2014;60:188-93.
2. Ideguchi M, Kajiwara K, Goto H, Sugimoto K, Nomura S, Ikeda E, *et al.* MRI findings and pathological features in early-stage glioblastoma. J Neurooncol 2015;123:289-97.
3. Oyama H, Ando Y, Aoki S, Kito A, Maki H, Hattori K, *et al.* Glioblastoma detected at the initial stage in its developmental process -case report. Neurol Med Chir (Tokyo) 2010;50:414-7.
4. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, *et al.* Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.
5. Tykocki T, Eltayeb M. Ten-year survival in glioblastoma. A systematic review. J Clin Neurosci 2018;54:7-13.
6. Adamson C, Kanu OO, Mehta AI, Di C, Lin N, Mattox AK, *et al.* Glioblastoma multiforme: A review of where we have been and where we are going. Expert Opin Investig Drugs 2009;18:1061-83.
7. Moskowitz SI, Jin T, Prayson RA. Role of MIB1 in predicting survival in patients with glioblastomas. J Neurooncol 2006;76:193-200.
8. Burger PC, Heinz ER, Shibata T, Kleihues P. Topographic anatomy and CT correlations in the untreated glioblastoma multiforme. J Neurosurg 1988;68:698-704.
9. Brandes AA, Franceschi E, Tosoni A, Benevento F, Scopece L, Mazzocchi V, *et al.* Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: Correlation with MGMT promoter methylation status. Cancer 2009;115:3512-8.
10. Zachariah MA, Oliveira-Costa JP, Carter BS, Stott SL, Nahed BV. Blood-based biomarkers for the diagnosis and monitoring of gliomas. Neuro Oncol 2018;20:1155-61.
11. Adachi-Hayama M, Adachi A, Shinozaki N, Matsutani T, Hiwasa T, Takiguchi M, *et al.* Circulating anti-filamin C autoantibody as a potential serum biomarker for low-grade gliomas. BMC Cancer 2014;14:452.