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Case Report

Surgically benign recovery and histopathologically malignant transformation of a gliomatosis cerebri after radiotherapy: natural course or an unpredictable desired effect?

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ABSTRACT

Gliomatosis cerebri is a rare primary glial neoplasm of the central nervous system characterized by excessive involvement of the brain tissue. Dispersion and infiltrative growth pattern of this insidious pathology limit the utility of total surgical removal and are underlying causes of its poor prognosis. Furthermore, unresponsiveness of gliomatosis cerebri to radiotherapy and its classification as high grade or type 2 is reportedly associated with poor long-term survival. Contrary to our current knowledge, we report the case of a 54-year-old male who was diagnosed with gliomatosis cerebri. He presented with an exceptional clinical and pathological course and poor prognostic factors but was successfully treated with total surgical resection after radiotherapy. The present case findings indicate the potential utility of surgery, usually underestimated, as a curative treatment for gliomatosis cerebri. Clinicians should be aware of negative predictive factors that may help identify a small subset of patients suitable for total surgical tumor removal, as in the present case.

Keywords: Gliomatosis cerebri, Malignant transformation, Radiotherapy, Total removal

INTRODUCTION

Diffuse, extensive infiltration of brain parenchyma with neoplastic glial cells histologically accompanied by involvement of at least three brain lobes, often extending to infratentorial structures, is the main pathological and descriptive feature of gliomatosis cerebri (GC).[1,2] While the anatomical integrity and architecture may be preserved and perceived in GC, widespread dispersion of this malignancy within the central nervous system, irrelevant of histopathological phenotype and grade, determines its diagnostic, therapeutic, and histopathological complexity.[3]

The management of GC is controversial, particularly regarding decisions on the initial or predominant treatment modality. Due to the diffuse infiltrative nature of GC, total tumor removal with good surgical outcomes is not typically considered feasible. Therefore, surgery is usually thought to be limited to diagnosis and is considered as a complementary component of a multidisciplinary therapy that comprises radiotherapy (RT) and chemotherapy.[4] However, regardless of treatment planning and modalities, clinical outcomes in patients with GC remain below expected levels, and the prognosis is poor with low survival rates.

Astrocytoma is the most common cellular phenotype of classical GC, while oligodendroglioma and mixed oligoastrocytoma are the other types, with relatively lower rates of occurrence.[5] Currently, for cases where diffuse astrocytoma presents as GC and total tumor removal cannot be achieved, radiotherapy is the most popular treatment option. Although RT has a considerable controlling effect on tumor growth,

malignant transformation of the primary tumor may be observed as a side effect that results in rapid clinical deterioration and shortening of life expectancy.[6] In the present report, we discuss the case of a male patient with GC considered to be surgically unresectable on initial evaluation. The tumor exhibited an astrocytic phenotype and was diagnosed as diffuse astrocytoma after stereotactic biopsy. The tumor subsequently became resectable after radiotherapy.

CASE REPORT

History and examination

A 54-year-old right-handed male was admitted to our hospital with a history of tonic-clonic seizures that had occurred three times in preceding 6 months. Physical examination was normal, and no neurological deficit was observed on admission. Ophthalmological examination did not reveal any evidence of papilledema, and no significant abnormalities were observed in laboratory studies.

Imaging

Previously-examined initial enhanced and non-enhanced cranial computed tomography revealed no pathological findings. After admission to our hospital for persistent seizures, the patient's initial magnetic resonance imaging (MRI) demonstrated a radiologically heterogeneous and infiltrative tumor accompanying a minimally edematous zone (Figure 1). The lesion was hypointense on T1-weighted imaging and did not show enhancement after gadolinium administration. On T2-weighted imaging, the lesion could be distinguished as a heterogeneous, diffuse, infiltrative hyperintensity in the temporoparietal subcortical white matter. The case was considered to be a low-grade glial tumor in light of the clinical history of generalized tonic-clonic seizures.

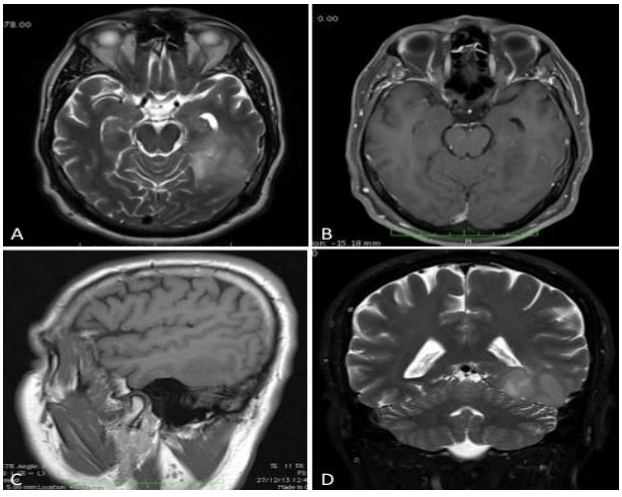

Figure 1: Patient's initial MRI showing heterogenic and infiltrative tumour on axial, sagittal and coronal T2 scans.

Management

In order to obtain evidence informing a definitive diagnosis and determine the most appropriate treatment option, the patient underwent a stereotactic tumor biopsy. A diagnosis of diffuse fibrillar astrocytoma (GC) was made according to histopathological findings (Figure 2). Considering the radiological characteristics of the lesion, including dispersed and infiltrative features with indefinite boundaries that may preclude surgical removal, radiotherapy was planned for both seizure control and slowing of tumor regression. The patient underwent whole brain RT accordingly. The radiation dose was 45 Gy administered as 1.8 Gy once a day, five fractions per week for approximately 5 weeks.

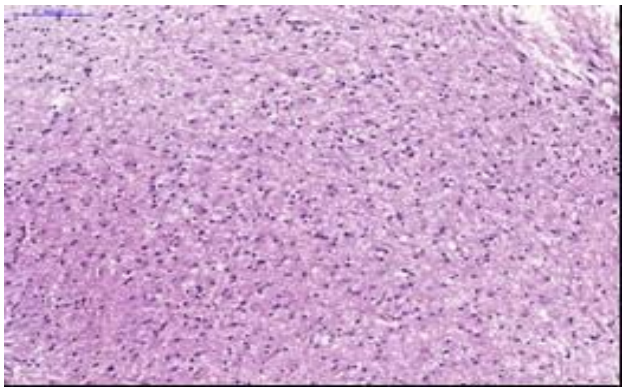

Figure 2: Histopathology of the specimen taken during the first operation (haematoxylin-eosin stain, X200). Tumour cells with moderately nuclear atypia and cellularity are present in fibrillary background, diagnosed as diffuse astrocytoma, grade II.

Three months after the stereotactic biopsy, RT was completed with no significant radiological changes observed on MRI. The patient was free of seizures with no neurological deficits were observed.

Five months after radiotherapy, the tumor was found to be easily distinguished radiologically with more definite boundaries (Figure 3). The patient underwent a left parietooccipital craniotomy with total removal of the tumor achieved. Re-examination of the histopathological diagnosis was found to support glioblastoma, grade IV (Figure 4).

After complete resection, the patient underwent re-irradiation with intensity-modulated RT. The target dose was administered to the isocenter at 54 Gy as 2 Gy once a day, five fractions per week. The defined target volume was encompassed by the 95% isodose. The gross tumor volume (GTV) was defined as the area of contrast enhancement on preoperative T1-weighted MRI sequences and surgical cavity. The clinical target volume (CTV) was defined as the GTV plus a margin of 5 mm and the planned target volume (PTV) as the CTV plus a margin of 5 mm. The patient also received daily

temozolomide (75 mg per square meter of body-surface area per day, 7 days per week, from the first to the last day of radiotherapy). After a 4-week break, the patient received six cycles of adjuvant temozolomide according to the standard 5-day schedule every 28 days.

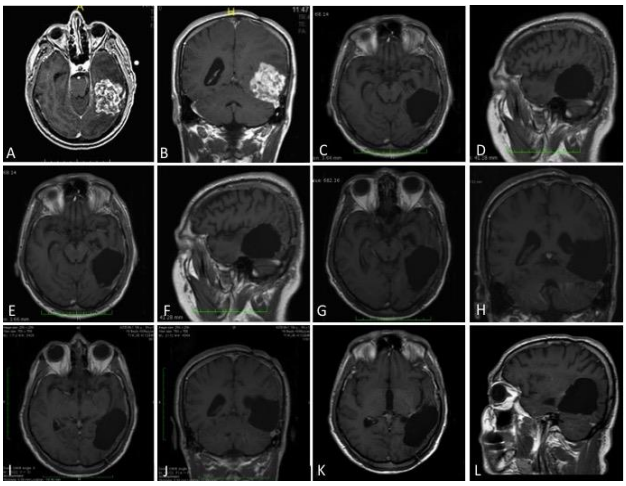

Figure 3: A, B: Pre-operative third MRI showing enlarged contrast enhancing mass. C-L: Post-operative follow-up MRIs showing no residue or recurrence.

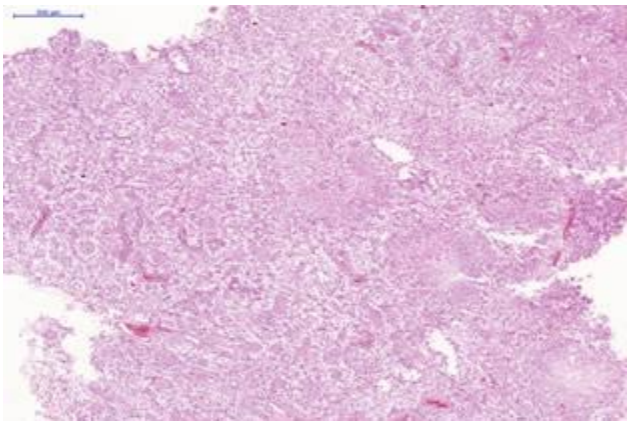

Figure 4: Histopathology of the specimen taken during the second operation (haematoxylin-eosin stain, ×35). Tumour showing marked cellularity, microvascular hyperplasia and pseudo palisading necrosis, diagnosed as glioblastoma, grade iv.

Post-operative course

The patient had no surgery-related neurological deficits and total removal of the tumor was confirmed with post-operative early MR imaging. The patient was discharged one week after surgery. Six months later, a scheduled MRI examination demonstrated no contrast enhancement indicative of any residual tumor or recurrence.

In the postoperative third year, during scheduled examinations, a temporal mass was found to be presented distant from and independent to primer surgical field. The newly formed lesion was totally excised with no complication or postoperative sequel (Figure 5).

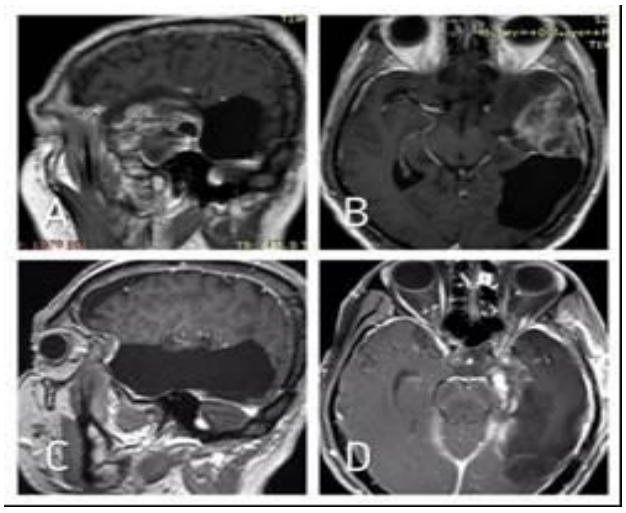

Figure 5: A, B: MRI of the patient in the third postoperative year showing newly formed temporal lesion.

DISCUSSION

Gliomatosis cerebri is a rare glial tumor characterized by diffuse in volvement of brain tissue with scattered neoplastic astrocytic elements.[7] According to the presence (type 1/classical form) or absence (type 2) of a discrete mass accompanying main neoplastic involvement, GC is classified into 2 groups.[8] Type 2 GC may form during the natural pathogenesis of type 1, with solitary lesions observed in addition to widespread background disease.[1] Although this classification depends on the radiological and macroscopic findings of the tumor, a supplementary definition for GC subtypes based on natural history and biological behavior divides tumor types into primary and secondary.[9] Whereas the primary subtype meets all the definition criteria of GC at the initial diagnosis, secondary GC forms as a new developed focal malignancy within a pre-existing neoplasm

There is no ideal or goal-oriented therapeutic procedure for the treatment of GC. Accordingly, either concomitant or separately, the use of multiple treatment modalities appear to stabilize tumor progression instead of being curative or eliminating the pathology entirely. In a relative large series of GC, surgical treatment was not reported due to the rarity of this condition and the lack of favorable conditions. Further, operative duration, indications, the extent of tumor removal, and need for subsequent surgery are other surgical issues that have not been highlighted or addressed in previous studies.

The major treatment modality for GC is based on radiotherapy followed by, or combined with, chemotherapy. Cranial radiotherapy in such patients is currently considered to be the treatment of choice.[10-13] Despite the described therapeutic effects of cranial

radiation, increased risk of delayed leukoencephalopathy in addition to neurocognitive disorders limit its potential beneficial effects. Besides, there is a high potential risk of dedifferentiation of the primary tumor to higher grades. Accordingly, the contribution of RT to overall survival in GC patients remains contentious.[3,12,14,15] However, the extent of tumor removal is reported to be associated with patient-reported outcomes and greater effect and efficacy of radiotherapy. Concerning the invasion of surrounding brain parenchyma by this type of tumor, total macroscopic removal with good patient outcomes is rarely seen. Recently, surgery has been posited to have utility for diagnosis or palliation only.

Due to a high tendency toward malignant transformation and histogenetical heterogeneity in the natural biological course of astrocytoma, growth rates, biological behavior, and tumoral grades may vary substantially. In particular, diffuse fibrillary astrocytomas, as in the present case, are at greater risk of dedifferentiating to higher grades. Secondary causes, such as radiotherapy or environmental factors, may underlie this process or this may be considered a normal stage of the natural pathogenesis of astrocytoma.

Chen et al. reported a study of more than 54 GC patients and demonstrated shorter survival than in previous literature among patients with astrocytic tumors of corresponding pathological grade.[16] In the present study, patients who underwent any form of surgical resection were found to have better overall survival compared to patients that underwent biopsy only; however, this difference was not statistically insignificant. According to a study by Park et al. in 33 patients with GC, 18 patients underwent craniotomy, 5 underwent biopsy, and the remaining patients underwent decompression and diagnosis.[17] In this study, dominant mass resection was also considered and mass formation was reported as a poor prognostic factor. In a review of these series, Type 2 GC was found to be correlated with poor survival and high-grade GC was posited to be associated with poor survival. In addition, Elshaikh et al have suggested aggressive therapy is required rather radiotherapy alone in patients with GC.[3]

In previous literature, cases that were initially diagnosed as GC before secondary glioblastoma formation after radiotherapy have been reported.[18] In these cases, mass lesions presented within previous lesions and were termed Type 2 GC. In contrast, in the present case, the initial lesion increased in size and formed a mass in an adjacent area previously free of neoplasia. It is difficult to determine whether this mass lesion formed due to radiotherapy or as part of its natural course. The findings of the present case demonstrate a mass lesion becoming amenable to total surgical removal due condensation of a previously unresectable tumor at the time of initial diagnosis. This "condensation result" describes radiological and macroscopic evidence of a previously uncircumscribed, dispersed, and infiltrative lesion. As a result of this formation, the tumor became amenable to surgical resection.

As an exhibited pathological phenotype of either GC or low grade glioma, fibrillary astrocytoma is defined as a diffusely infiltrating tumor in a group of diffuse low grade glial tumors (DLGG) with oligodendrogliomas and oligoastrocytomas.[5] The distinctive feature of this group, as it is understood from the term "diffuse," is aggressive invasiveness and progressive behavior.[19] As with GC, such tumors grow progressively, follow the white matter tracts, and have a higher incidence of progression to higher grades.[20] The optimal management of low-grade glial tumors and diffuse fibrillary astrocytoma is surgical excision with an aim for total removal. Similarly, to these tumors alone, corresponding grade and histopathological type of GC should be evaluated in correlation.

There are many publications addressing the issue of malignant transformation of LGG tumors due to radiation; however, the most important feature of the present case is the optimized conditions for surgery after radiotherapy, which was not favorable at the time of diagnosis.[21] As explained in detail above, the radiological characteristics of the tumor at initial diagnosed were not amenable to surgery as an alternative or initial treatment.

Regardless of the pathophysiological cause, either due to the natural course of LGG tumors or radiotherapy, patients should be followed up at frequent intervals for clinical and radiological examinations. In terms of radiotherapy, the performance of an initial stereotactic biopsy does not mean that surgery should be excluded as a potential treatment option but should be kept as a favorable option during follow up.

In the third year of follow up in the present case, a huge mass lesion was detected on MRI. Due to the lack of previous evidence of an invasive lesion or any surrounding diffuse pathology, we believe the second lesion did not represent a type 2 GC. In contrast to all the previously described poor prognostic factors, the patient remained tumor-free over a follow up of 2 years.[6,22] According to current knowledge, the malignant transformation of previously benign tumors may result in well-circumscribed lesions that satisfy surgical criteria and be evaluated as having a good prognosis, as in the present case.

The findings of the present case highlight the need for patient and pathology based algorithms for the treatment of GC. As the most determining prognostic factor is the proportion of tumor removed surgically, surgery should be always considered, even in cases with tumors appearing unresectable. The present report distinctly emphasizes that a triple treatment modality, consisting of radiotherapy, stereotactic biopsy, and surgery, should be taken into consideration during the diagnosis, treatment, and follow-up stages of the management of GC to improve quality of life and patient outcomes.

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