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Case Report

CASE REPORT

Presentation of treatment effect in glioblastoma after dose-escalation radiation therapy

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Abstract

Glioblastoma is the most aggressive primary brain tumor in adults. Limited treatment options and the intense nature of therapy make determining the appropriate treatment course for each patient difficult. The appearance of transient worsening of imaging findings, known as treatment effect, after chemoradiation further complicates clinical decision-making. Accurately differentiating treatment effects from true progression is critical as subsequent treatment decisions are based largely on radiographic evidence of tumor progression. As chemoradiation can cause worsening of imaging findings, it is possible that the use of new treatments and modified chemoradiation regimens may alter the presentation of treatment effect. Therefore, physicians should be aware that atypical presentations of treatment effects can occur, and may be more likely, when treatment regimens are modified. Here, we present the case of a patient with isocitrate dehydrogenase 1 wild type, O-6-methylguanine-DNA methyltransferase-methylated glioblastoma who underwent dose-escalation radiation therapy (to 75 Gy) and exhibited worsened imaging findings at 8 months post-radiation.

INTRODUCTION

Glioblastoma (GBM), the most common primary malignant brain tumor in adults, is exceptionally aggressive and often resistant to treatment [1]. The classic standard of care for GBMs is maximal safe surgical resection with subsequent radiotherapy and concurrent temozolomide (TMZ), an alkylating agent, followed by typically 6 cycles of adjuvant TMZ [2]. Despite this multimodal treatment regimen, virtually all patients experience tumor progression with a median survival of 15 months [3].

Worsening imaging findings after brain tumor treatment are common and are often manifested by new or worsening edema and contrast enhancement on MRI [4, 5]. When these findings are transient and occur within the first 90 days after completing radiation therapy, they are often described as pseudoprogression. Later manifestations of treatment are commonly referred

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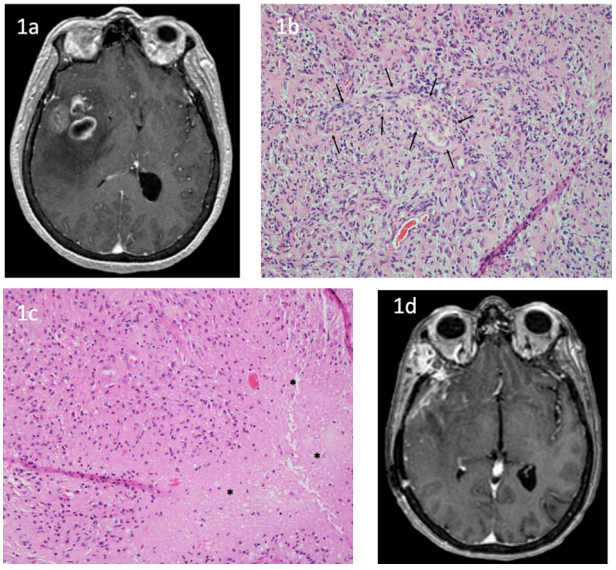

Figure 1: Initial imaging and histopathology. (**a**) Post-contrast enhanced T1-weighted MRI indicated a lesion in the temporal lobe at the time of initial presentation. (**b** and **c**) H&E stains showing sheets of atypical glial cells with irregular hyperchromatic nuclei and eosinophilic cytoplasm. WHO grade IV designation was rendered due to the presence of microvascular proliferation (b, arrows) and necrosis (c, asterisks). Formalin-fixed paraffin-embedded (FFPE) human tissue, 5-µm-thick sections, ×200 magnification. (**d**) Post-contrast enhanced T1-weighted MRI 5 weeks post-surgical resection.

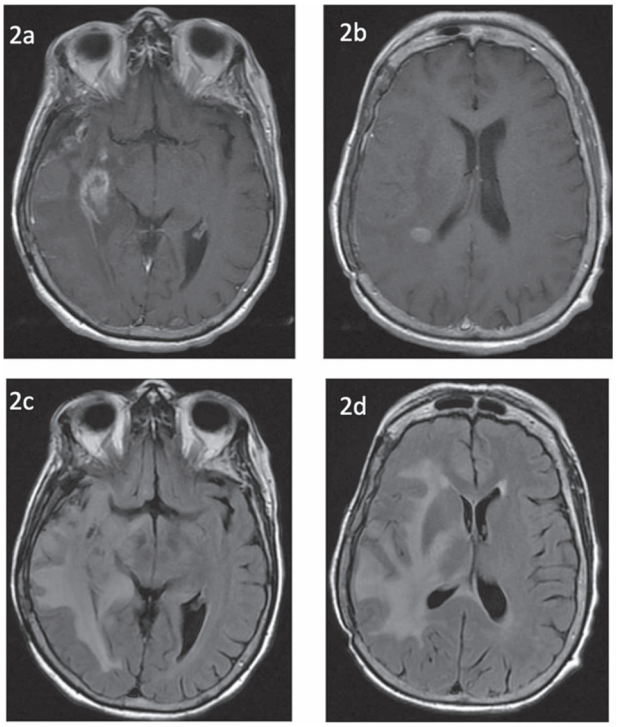

Figure 2: Imaging 8 months post-chemoradiation. (**a**) Post-contrast T1-weighted MRI reveals increasing enhancement in the right temporal lobe. (**b**) Post-contrast T1-weighted MRI reveals new enhancement in the right parietal lobe surrounding the lateral ventricle. (**c**) FLAIR imaging reveals diffuse hyperintensity unresolved since treatment. (**d**) FLAIR imaging reveals worsening mass effect on the lateral ventricles.

to as radiation necrosis. These treatment effects can make imaging difficult to interpret, and often the true cause of worsening imaging may not be known until delayed follow-up is performed or tissue is sampled via biopsy. Here, we report the case of a 64-year-old female who underwent dose-escalation radiation therapy for GBM and developed robust treatment-related worsening of radiographic findings, i.e. a treatment effect, and some investigators might also describe this as a 'pseudoprogression,' 8 months post-chemoradiation.

CASE REPORT

A 64-year-old female presented with new-onset altered mental status. Contrast-enhanced MRI revealed a 5.1-cm lesion in the right temporal lobe (Fig. 1a). Three days later, the patient underwent surgical resection and histopathology (Fig. 1b and c) confirmed a diagnosis of GBM. Imaging 5 weeks post-surgery is shown for reference (Fig. 1d). Genetic analyses indicated that the tumor was O-6-methylguanine-DNA methyltransferase (MGMT)-hypermethylated and isocitrate dehydrogenase 1 wild type.

After surgical resection, the patient began a 6-week treatment regimen of TMZ with concurrent radiation as part of a dose-escalation radiation clinical trial (NCT03137888) in which the patient received doses up to 75 Gy to regions identified as high risk for recurrence based on areas of metabolic abnormality on spectroscopic MRI [6]. Subsequently, she was continued on TMZ maintenance therapy. However, due to hematological toxicity including thrombocytopenia, Cycles 2 and 3 of maintenance TMZ were delayed. Six months after completing radiation, tumor-treating fields were added to her treatment regimen.

Eight months after the completion of radiation therapy, an MRI scan revealed a new enhancing region in the temporal lobe near the original tumor site (Fig. 2a) and a new punctate focus of enhancing in the right parietal lobe surrounding the posterior horn of the right lateral ventricle (Fig. 2b), both within the field of radiation treatment. Coupled with diffuse hyperintensity on FLAIR imaging (Fig. 2c) and lateral ventricle compression (Fig. 2c and d), these findings raised concerns for tumor progression. At this time, the patient was asymptomatic and on Cycle 8 of TMZ, but had stopped tumor-treating field treatment.

One month after imaging concerning progression, the patient underwent surgical excision of the right temporal lesion. Histopathology revealed vascular hyalinization and a lack of palisading-type necrosis (Fig. 3a), which suggested predominantly post-treatment effects. Extensive necrosis was present (Fig. 3b), with an estimated 20% viable tumor and 80% therapy effect.

Imaging 1 month post-surgery revealed reduced T1 enhancement in the temporal lobes (Fig. 4a and b), and although confluent hyperintensity remained, ventricular compression had resolved (Fig. 4c and d) consistent with improving treatment-related changes.

Because the pathology results revealed predominantly treatment effects, the patient was not considered a treatment failure and was continued on TMZ. One year and three months post-diagnosis, the patient continues to be treated with TMZ without further progression.

DISCUSSION

Worsening of imaging findings after completing chemoradiation is a common radiological finding in GBM patients. As

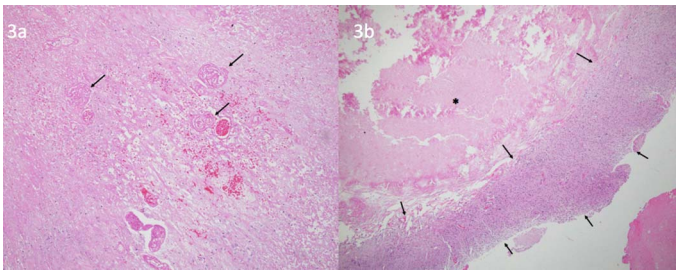

Figure 3: Histopathology of glioblastoma resection after surgery 1 year post-diagnosis. (**a**) H&E stain showing extensive necrosis and hyalinized vessels (arrows) consistent with therapy effect. Viable glioblastoma is not apparent in this field. Formalin-fixed paraffin embedded (FFPE) human tissue, 5-µm-thick sections, ×100 magnification. (**b**) H&E stain showing extensive necrosis (asterisks) and a rind of viable glioblastoma (arrows). FFPE human tissue, 5-µm-thick sections, ×40 magnification.

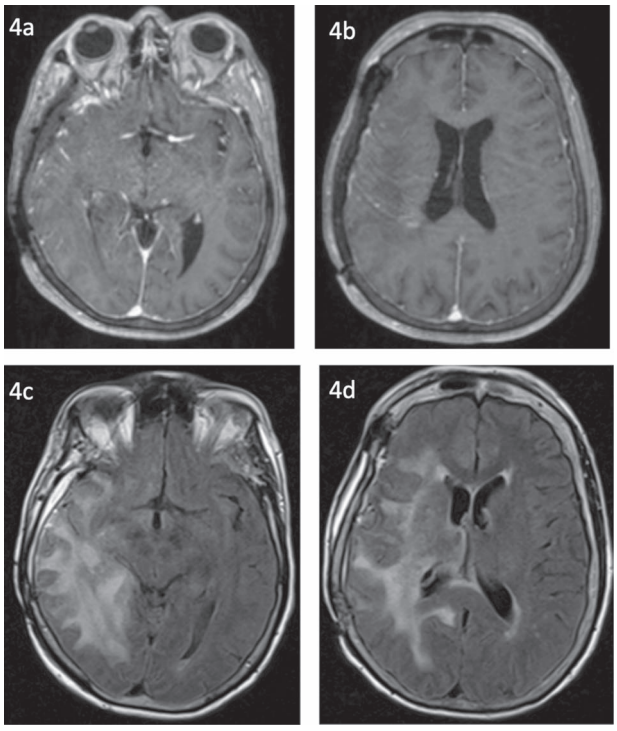

Figure 4: Post-surgical imaging 1 month after imaging suggestive of treatment effect. (**a**) Post-contrast enhanced T1-weighted MRI indicates resolution of enhancement in temporal lobe. (**b**) Post-contrast enhanced T1-weighted MRI indicates weakening of enhancement adjacent to the lateral ventricle. (**c**) FLAIR imaging reveals confluent white matter hyperintensity. (**d**) FLAIR imaging reveals improving mass effect on the lateral ventricle.

many as 91% of patients with MGMT hypermethylation exhibit pseudoprogression, an early form of treatment effect, following concurrent radiation and TMZ administration [7]. Unfortunately, it is difficult to distinguish treatment effect from tumor progression based solely on a single post-chemoradiation MRI as both present on imaging as worsening contrast enhancement and T2/FLAIR hyperintensity. Treatment effect cannot be definitively diagnosed until either follow-up imaging reveals that the apparent progression has resolved or a surgical biopsy of the area provides histopathological confirmation. Due to the high incidence of treatment effect and difficulty distinguishing it from tumor recurrence with conventional imaging, it has been suggested that no new treatment be initiated on the basis of apparent tumor progression within the field of radiation on MRI if the patient is asymptomatic [4].

Here, we report a case of GBM with imaging worsening that occurred 8 months after the conclusion of dose-escalated radiation with concurrent chemotherapy. Most clinical trials have found radiation dose escalation to have no effect on survival, although new trials are utilizing sophisticated imaging like spectroscopic MRI to target the elevated radiation to areas at high risk for recurrence [8]. The present example of imaging changes and histopathology in a MGMT-methylated patient that underwent dose-escalation therapy may be useful in identifying delayed treatment effect in other patients undergoing atypical treatments. The incidence of treatment effect may increase with higher radiation doses and fraction sizes [9]; thus, it is likely that this patient's treatment course, which included participation in a dose-escalation clinical trial involving boosted radiation doses up to 75 Gy, precipitated this atypical presentation of a treatment effect resembling pseudoprogression well beyond the typical 90-day window.

Accurately differentiating post-treatment effects from tumor progression is critical for subsequent decisions regarding treatment course. If worsening findings are likely to be treatment effect, continued adjuvant TMZ is warranted. A corticosteroid and/or other therapies including a VEGF inhibitor may be administered to counteract inflammation and cerebral edema if the patient is symptomatic [4, 10]. In contrast, tumor progression may require new treatment options including a second surgical resection, re-irradiation, tumor-treating fields, supportive care and/or enrollment in a clinical trial [10]. Additionally, the proper identification of treatment effects is critical both for adhering to inclusion criteria and for establishing patient baselines in clinical trials. It is therefore crucial for physicians to be mindful that various presentations of chemoradiation-related changes, such as described here, can occur and perhaps are more likely in cases with atypical treatment regimens.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest.

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ETHICAL APPROVAL

None required.

CONSENT

Written informed consent was obtained from the patient for this case report.

GUARANTOR

The last author of this study (S.S.) guarantees for the accuracy of this case report.

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