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Case Report

Recurrent Glioblastoma Multiforme: Implication of Nonenhancing Lesions on Bevacizumab Treatment

Daniela Alexandru[1], Hung-Wen Kao[2, 5], Ronald Kim[3], Mark E. Linskey[1], Anton N. Hasso[2], Daniela A. Bota[1, 4]

Departments of Neurosurgery[1], Radiological Sciences[2], Pathology[3], and Neurology[4], University of California, Irvine Medical Center, Irvine, CA, USA
Department of Radiology[5], Tri-Service General Hospital, National Defense Medical College, Taipei, Taiwan

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Corresponding Author:
Daniela Alexandru,
Departments of Neurosurgery, University of California, Irvine Medical Center, Irvine, CA, USA
danielaa@uci.edu

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Abstract

Glioblastoma multiforme (GBM) is the most common primary brain tumors, accounting for 15-20% of all intracranial tumors. It is one of the most lethal tumors of the central nervous system with a median survival from diagnosis on the order of 6 to 18 months. Despite aggressive resection and chemoradiation, the tumor always recurs. Magnetic Resonance (MR) imaging is an essential component in the diagnosis, treatment planning, and following response. However, the imaging features of recurrent GBM may be challenging, particularly in patients undertaking novel antiangiogenic therapy. We present such a case treated with repeated surgeries, combined chemoradiation, and bevacizumab. The patient benefited from the regimen with a 6-month progression-free survival, evidenced on both stable clinical condition and MR imaging findings. However, despite chemotherapy, a fulminant progression developed with growth multiple tumors in different locations and variable imaging characteristics, ranging from typical enhancing nodules to nonenhancing signal changes. The lesions of different imaging features were biopsy-proved to be recurrent GBM. We discuss the use of MR imaging in the evaluation of GBM treated with bevacizumab and emphasize the implication of signal abnormality on fluid-attenuated inversion recovery (FLAIR) images for early evidence of recurrence.

INTRODUCTION

Glioblastoma multiforme (GBM), the most aggressive tumor of the central nervous system in adults, is highly resistant to chemotherapy and radiotherapy and exhibits robust angiogenesis, resistance to apoptosis and propensity to necrosis. The traditional chemotherapies rely on DNA damage and disruption of mitotic machinery with limited effect on prolonging patient survival [1]. The reported data showed a 6-month progression-free-survival of 15% and median progression-free survival of only 9 weeks among 225 patients of recurrent GBM treated with traditional chemotherapy [2]. Upon progression, patients typically develop progressive physical and mental debilitation culminating in death 40 to 50 weeks from diagnosis. Novel target therapies were developed to interrupt specific molecular mechanisms involved in abnormal signaling and resistance to apoptosis. The recent phase II trial of antiangiogenic agent bevacizumab is a monoclonal antibody developed to impede tumor progression and increase survival by blocking the vascular endothelial growth factor (VEGF), which is highly expressed in malignant gliomas [3-6]. In addition, inhibition of VEGF receptor signaling was shown to reverse the resistance of GBM to radiotherapy in a preclinical study [7]. The combination of bevacizumab and irinotecan resulted in a 6-month survival of 72% with small risks of life-threatening complications, such as thromboembolic disease and hemorrhage [8, 9].

MR imaging has been used as a biomarker for treatment response of GBM. Post-contrast T1-weighted imaging (T1WI) is the current standard to determine therapy efficacy, criteria extrapolated from Macdonald et al [10]. Response in this scheme is based on major changes in enhancing tumor size observed on imaging. However, contrast enhancement of tumor is nonspecific and depends on abnormal vascular architecture and disrupted integrity of the blood-brain barrier (BBB), which may be modified by antiangiogenic agents. Recently in the study of Norden et al, bevacizumab was shown to have possible effect on MR imaging patterns of recurrence through decreasing capillary permeability of the BBB [11]. Adding to the complexity of MR imaging, infiltrative high-grade gliomas do not always result in disruption of the BBB. As a result, there exists

a discrepancy between tumor progression and MR imaging findings, particularly when using the traditional imaging criteria. We present a case with recurrent GBM treated with bevacizumab and chemotherapy with different imaging features of different recurrent lesions. The implication of the MR imaging finding is emphasized for monitoring the treatment efficacy of this novel target therapy.

CASE REPORT

A 51-year-old man presented with generalized weakness, syncope, and new-onset seizures in February 2008. Physical examination revealed no neurological deficit. He had no history of malignancy or significant medical condition. MR imaging of the brain showed an enhancing tumor in the right temporal lobe. He underwent surgical resection of the tumor in March 2008 and found GBM on pathological examination. One year after the initial surgery, MR imaging showed a thick irregular increased signals with nodular enhancements on the edge of the surgical cavity (Figure 1). A second surgery confirmed the diagnosis of recurrent GBM in April 2009 followed by treatment with concomitant radiation and temozolomide-based chemotherapy. After completion a full course of radiotherapy, he received two more cycles of temozolomide. Three months later, unfortunately, thick irregular increased signal intensity appeared on the posterior margin of the surgical cavity with extension to the hippocampus and presence of nodular enhancements (Figure 2). Then he started a standard treatment for recurrent GBM with intravenous bevacizumab and irinotecan every two weeks for 7 cycles. Contrast-enhanced MR imaging of the brain was performed every 2 months for follow-up.

He was free of neurological symptoms and imaging evidence of disease progression in the following 6 months until two indistinct non-enhancing lesions developed in the body and right aspect of the splenium of the corpus callosum (Figure 3). However, the right temporal lobe remained stable evidenced by diminished abnormal signal on FLAIR images and absence of contrast enhancement. To our surprise, he had stable neurological condition in the next 5 months, while multiple areas of abnormal signals bloomed in the right hemisphere, including the middle frontal lobe, orbitofrontal lobe, hippocampus, occipital lobe, and areas around the surgical bed in the temporal lobe (Figure 4). Not all the lesions shared similar imaging characteristics. A lesion deep in the surgical margin showed avid nodular contrast enhancement and a patchy nodular enhancement appeared in the periventricular white matter of the right occipital lobe with subependymal extension to the lateral ventricle nearby. The rest of the lesions were not enhancing, including the two corpus callosum ones, which were significantly enlarged and infiltrative. In June 2010, biopsy of the brain was performed in five different locations, including body and splenium of the corpus callosum, right frontal lobe, and enhancing areas in the right temporal and occipital lobes (Figure 4). The specimens all turned out to be GBM on pathological examinations (Figure 5). During the following 2 months, the patient's functional status declined rapidly. At the same time the tumors drastically grew with more avid contrast enhancements and areas of necrosis.

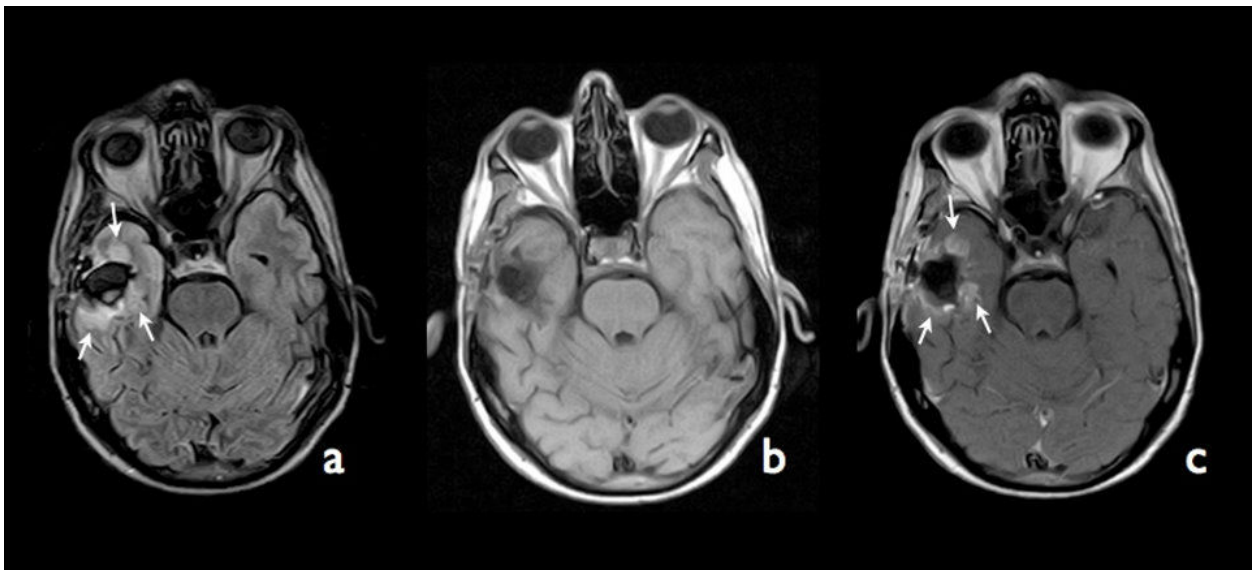

Figure 1. One year after initial surgery, FLAIR image (a) showed an irregular rim of increased signal (arrows) around the surgical cavity in the right temporal lobe. The lesions appeared iso- to low signal on T1WI (b) and nodular enhancements on post-contrast T1WI (c).

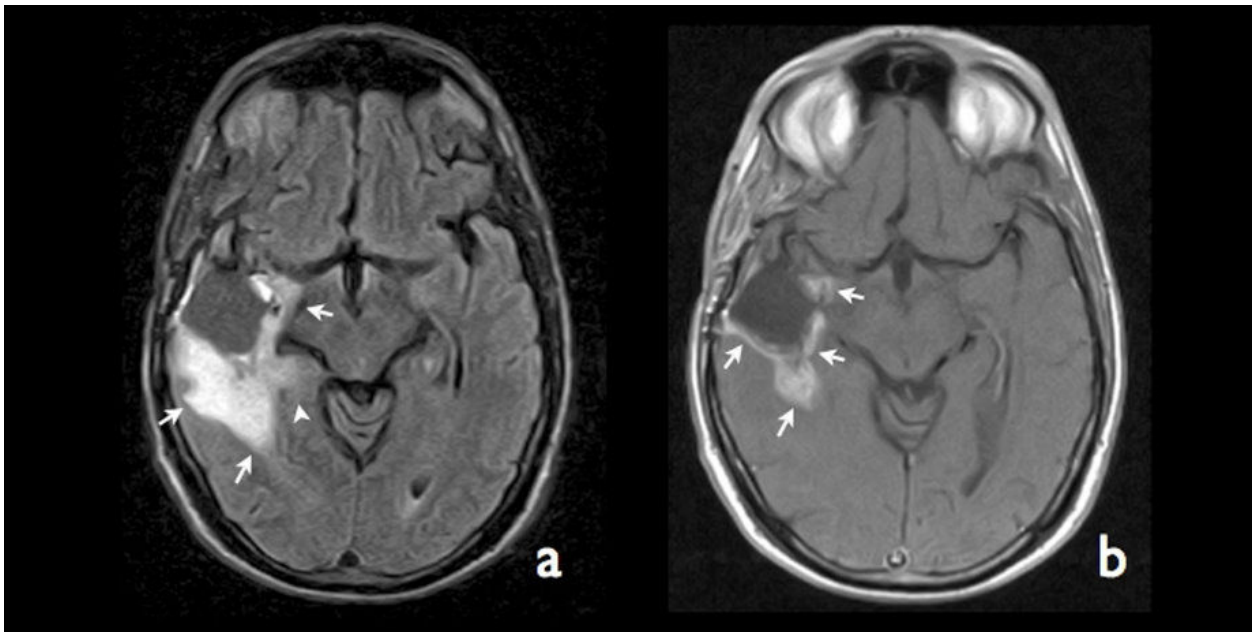

Figure 2. On FLAIR image (a), a thick irregular high-signal rim (arrows) was noted around the surgical margin with extension to the hippocampus (arrowhead). T1WI (b) showed linear enhancements around the surgical cavity and a nodule posteriorly (arrows).

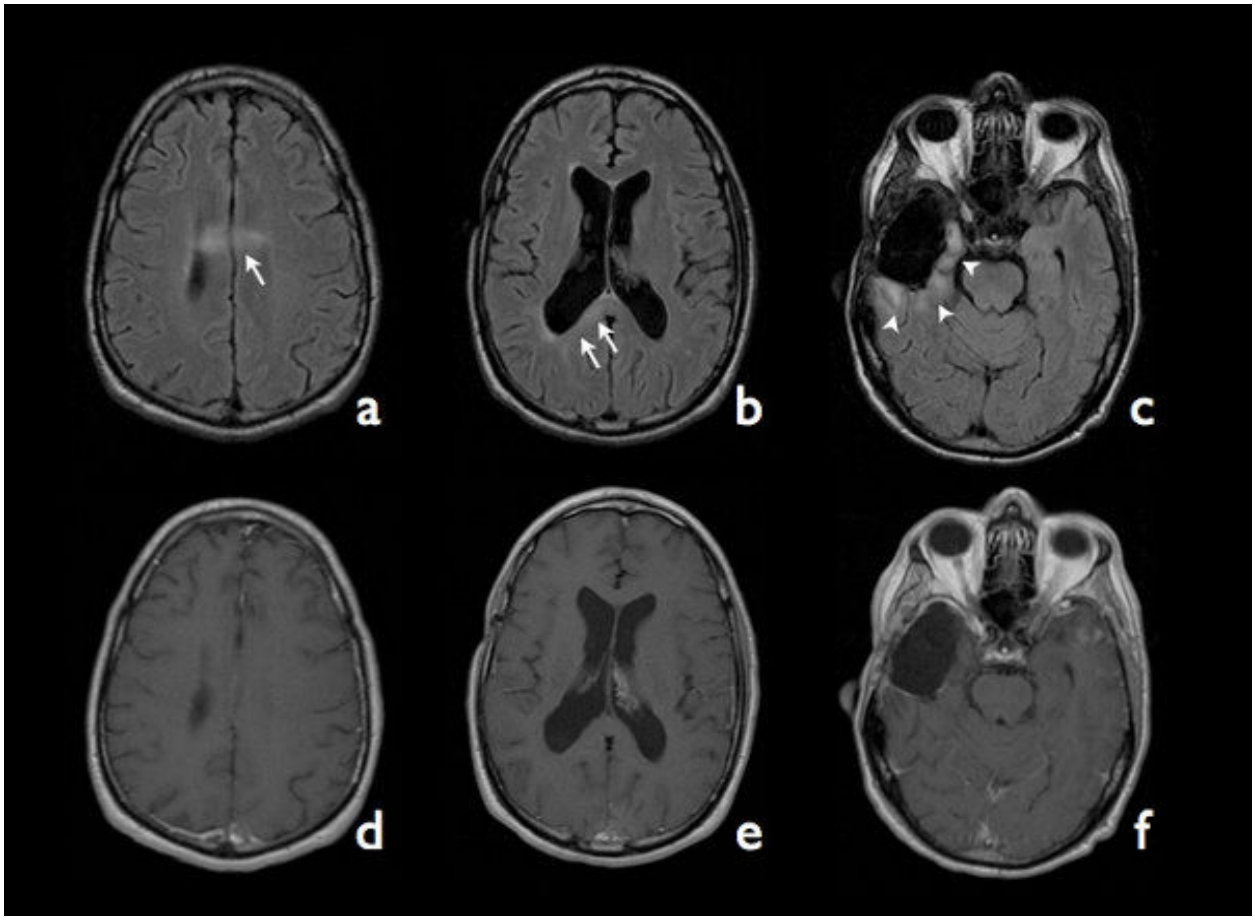

Figure 3. Six months after starting of bevacizumab treatment, FLAIR images (a, b, c) demonstrated two indistinct increased signals in the body and right aspect of the genu of corpus callosum (arrows) as well as diminished signal around the surgical cavity (arrowheads). None of the lesions were enhanced on post-contrast T1WI (d, e, f).

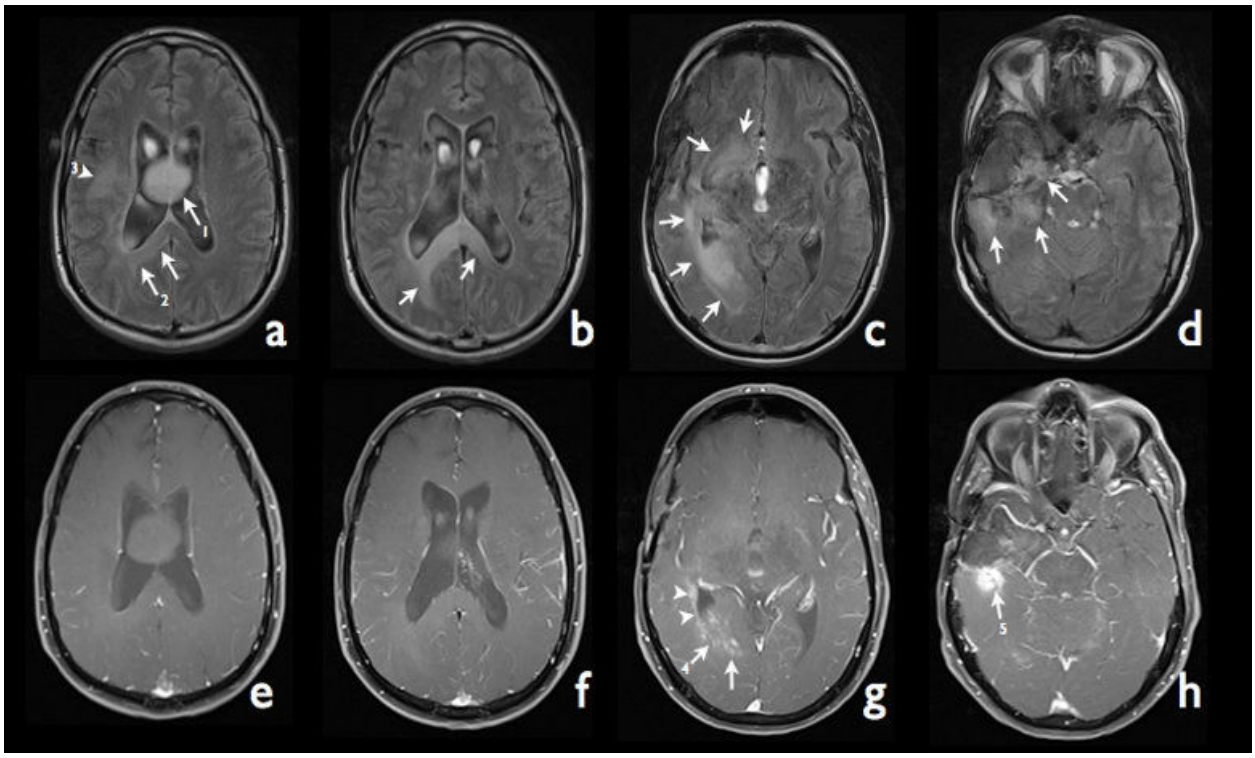

Figure 4. Five more months after discovery of the abnormalities in the corpus callosum, FLAIR images (a, b, c, d) depicted significant enlargement of the lesions in the corpus callosum (arrows in a) with extension to the left aspect of the genu and right occipital periventricular white matter (arrows in b). Also noted was a newly developed nonenhancing lesion in the right middle frontal white matter (arrowhead in a). Around the surgical cavity showed a thick rim of irregular increased signal involving the orbitofrontal lobe, hippocampus, temporal lobe and occipital lobe (arrows in c and d). Post-contrast T1WI (e, f, g, h) delineated a patchy nodular enhancement (arrows in g) around the occipital horn of the right lateral ventricle with subependymal tumor extension (arrowheads in g) and a solid enhancing nodule (arrow in h) in the posterior margin of the surgical cavity. The rest of the lesions were not enhancing. Stereotactic biopsy was performed in five locations (denoted with numbers 1 to 5).

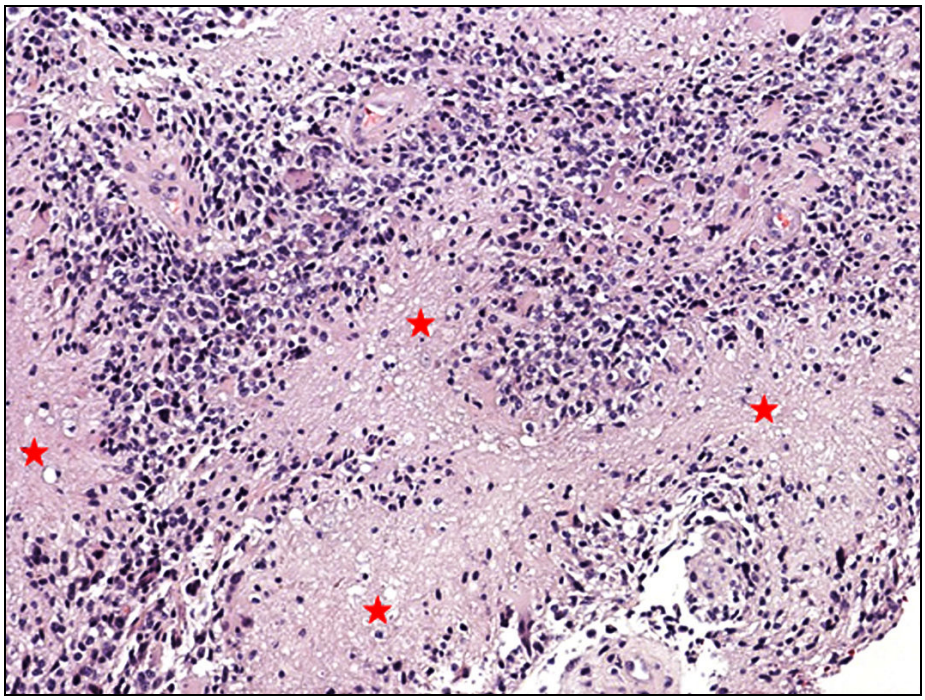

Figure 5. Pathology of the specimen confirmed the diagnosis of GBM with hyperchromatic and highly pleomorphic cells pseudopalisading around areas of alternating necrosis (stars) (H&E, x 100).

DISCUSSION

Composed of a heterogeneous mixture of poorly differentiated astrocytes, GBM is World Health Organization grade IV tumor with high mitotic activity and either endothelial proliferation or necrosis. Patients with GBM are best treated with a combined modality approach, including maximal safe tumor resection followed by radiotherapy with concurrent and adjuvant temozolomide [1, 12]. However, most patients eventually develop progressive or recurrent disease despite aggressive therapies. For recurrent GBM, the published experience with bevacizumab and chemotherapy showed at least 50% of radiographic response rates and median progression-free survival of 24 weeks [13]. However, the antiangiogenic effect on the tumor vasculature are usually mistakenly referred to as tumor responses because the traditional method of evaluating tumor response and progression was based on tumor size observed on post-contrast MR imaging through a disrupted BBB, which may be modified by bevacizumab [14].

In our case, repeated surgical resections of the tumor in the right temporal lobe were performed followed by temozolomide-based chemoradiation, which stabilized the patient for only 3 months until enhancing nodules appeared around the resection bed (Figure 2). The subsequent recurrent tumors had enhancing characteristics of the initial recurrent ones (Figure 1). Despite aggressive therapy with bevacizumab and irinotecan, the tumor progressed for the third time with MR imaging patterns quite different from the previous two recurrent episodes (Figures 3 and 4). It has been known that local recurrences predominate after the temozolomide-based chemoradiation while distant recurrences tend to occur later in patients with longer survival time [15, 16]. This may be the nature course of these patients living long enough to develop distant recurrences. However, complex interaction between therapies and tumor genomics may also play a role in the presentation of tumor recurrence.

Norden et al categorized MR imaging findings of GBM recurrence into three patterns: 1) Local recurrence, defined as increased enhancement developed in contiguity with the original tumor; 2) distal recurrence, new foci of enhancement distant from the original area of enhancing tumor; 3) diffuse recurrence, at least 25% increased in area of abnormal FLAIR hyperintensity while local tumor mass remains stable [11]. Our case showed local recurrences in the first and second recurrences. After treatment with bevacizumab, distant recurrences occurred early in the corpus callosum and right middle frontal lobe followed by diffuse and local recurrences in contiguity with the surgical cavity. A higher likelihood of diffuse or distant recurrence was documented in bevacizumab-treated patients than in controls, treated with conventional chemotherapy alone [11]. The change of enhancing pattern in the distal and diffuse recurrences may result from the antiangiogenic effect of bevacizumab. In two series of Norden et al, the nonenhancing lesions on FLAIR or T2-weighted images were "suspected" to be recurrences rather than pathologically proved [11, 17]. Our case not only pathologically proved the FLAIR abnormalities to be recurrent GBM but also demonstrated the existence of nonenhancing distal recurrences, which were not documented in previous studies [11, 17, 18].

The abnormal FLAIR hyperintensities may not only reflect infiltrating tumor but also peritumoral edema or radiation change. In particular clinical setting such as in our case, it may be difficult to differentiate one from another. However, bevacizumab's antiangiogenic effect usually reduces peritumoral edema. Newly developed high signal intensities on FLAIR images may mainly reflect tumor infiltration and should raise a high index of suspicion until proven otherwise. Therapeutic effect of radiation therapy may also lead to the presence of nonenhancing FLAIR abnormal signal intensities in the corpus callosum. But they rarely appear in the absence of diffuse abnormal signal intensities in the deep white matter [19].

In conclusion, MR imaging findings of recurrent GBM vary widely on bevacizumab treatment, raging from enhancing local recurrent nodules to nonenhancing distant abnormal FLAIR signal intensities, even in one single case. Awareness of these bizarre imaging findings may facilitate early diagnosis and treatment of recurrent GBM.

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