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Treatment-Related MR Imaging Findings in Patients with Glioma after Radiotherapy, Chemotherapy, and Biological Therapy

*Xiao Li and Fanny Morón**

Department of Radiology, Baylor College of Medicine, USA

Abstract

Patients undergoing radiotherapy, chemotherapy, and biological therapy demonstrate treatment-related changes and characteristic magnetic resonance imaging findings. By understanding the various imaging findings, better clinical decisions can be made.

Glioblastoma is the most common malignant primary brain tumor. Current standard of care involves surgical resection with first line radiation therapy and concomitant/adjuvant temozolomide chemotherapy and second line anti-angiogenic therapy, bevacizumab, for recurrent glioblastoma. Macdonald's criteria were commonly used for assessing treatment response to high-grade glioma therapy. Limitations to these criteria led to the more updated response assessment in neuro-oncology criteria.

Intracranial and regional radiation to the brain often produces a number of significant changes that complicate the assessment of post-treatment outcomes. Leukoencephalopathy is often seen post-radiation therapy because white matter is particularly vulnerable to radiation. Radiation necrosis and tumor reoccurrence can both present with contrast enhancement, mass effect and vasogenic edema. Other post-radiation therapy changes include radiation-induced meningioma, cavernous malformation, and micro bleeds.

Chemotherapy and biological therapy treatments also create difficulty in post-treatment response interpretation. For example, pseudop rogression is non-tumoral enhancement likely associated with inflammatory local tissue reaction and edema caused by treatments such as temozolomide. On the other hand, pseudo response is post-treatment decrease in contrast enhancement not associated with true tumor reduction.

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Correspondence:
Fanny Morón, Department of Radiology, Baylor College of Medicine, Houston, TX, US, One Baylor Plaza, Houston, TX 77030, USA, E-mail: xiaol@bcm.edu; fmoron@bcm.edu

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Introduction

To provide a mini-review of the various treatment related changes and characteristic MR imaging findings in patients with glioma after undergoing radiotherapy, chemotherapy and biological therapy.

Materials and Methods

A literature review was performed to discuss the treatment changes and imaging appearances followed by a pictorial essay of selected examples.

Results and Discussion

Treatment for malignant neoplasm such as glioblastoma has been standardized with surgery, radiation treatment and temozolomide. In 2009, Bevacizumab was approved for recurrent glioblastoma. Historically, Macdonald's criteria were used to assess treatment response based on tumor size on Magnetic Resonance (MR), clinical assessment, and corticosteroid use [1]. However, Macdonald's criteria were limited because it only factored in the contrast-enhancing tumor component and did not adequately deal with pseudo progression and pseudo response, discussed later. Response Assessment in Neuro-oncology criteria (RANO) were created as an updated guideline by taking into account the non-enhancing tumor component [2,3]. Patients undergoing radiotherapy, chemotherapy, and biological therapy demonstrate the following treatment-related changes and characteristic MR imaging findings.

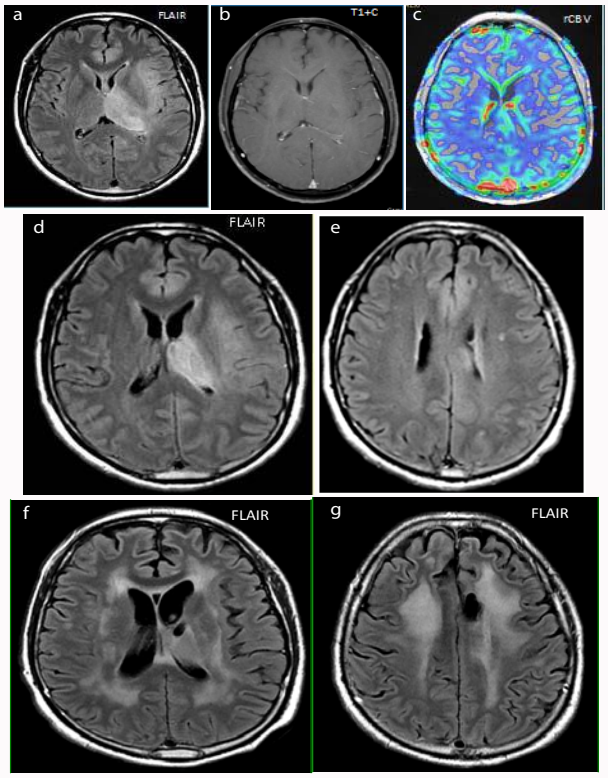

Figure 1a-c: At presentation, FLAIR hyperintense, but non-enhancing on post contrast T1W images and, non-hyperemic infiltrating glioma (no increase in rCVB).
Figure 1d-e: 2 years after whole brain radiation and boost to the left thalamus plus TMZ shows mild progression of perilesional and white matter FLAIR hyperintensity, also new mild generalized brain volume loss.
Figure 1f-g: 3 years after radiation with progression of atrophy and confluent FLAIR hyperintensity

Radiation-related treatment effects

Radiation therapy is typically administered 5 days a week for 6-7 weeks until a dose of 60 Gy is reached. The radiation target dividing cells directly and indirectly leading to vasodilation, disruption of the blood brain barrier, and edema [3]. This leads to vascular damage, endocrine disturbance, and neural structural fibrosis [4].

There are multiple phases of radiation injury. Acute phase of radiation injury occurs during or shortly after radiation with only focal damage with reversible glial glycogen depositions. The sub acute phase occurs up to 12 weeks after radiation with cell death of myelin-producing oligodendrocytes that followsremyelinization of the brain tissue. The chronic phase occurs months to years after completing radiation with diffuse changes due to wall thickening of the vascular structures, decreasing number of glial-supporting cells, and diffuse demyelinization [1,3,5,6].

Enhancement on MR can also be caused by many factors from tumor reoccurrence to inflammation (treatment-related), post-surgical changes, ischemia, and radiation effects [3]. Post-surgical enhancement possibly due to ischemic changes may occur shortly after the procedure and can last sub acutely up to 2-3 months [3]. Two major findings that can come about after radiation are leukoencephalopathy and radiation necrosis.

Leukoencephalopathy often develops months to years after treatment. This can be accompanied by chronic mental status impairment with progressive cognitive decline and personality changes [4]. It is often seen in post-radiation therapy and exacerbated in combination with chemotherapy. MRI findings include progression of white matter confluent FLAIR hyperintensity, progressive atrophy, and transient areas of white matter enhancement [7] (Figure1). Ventricular dilation, cerebral atrophy, and areas of focal enhancement may also be seen which can lead to weakness, dementia, and death [4].

Radiation necrosis has an incidence of 3-24% and often occurs 3-12 months after treatment, but can also present up to decades later [8]. The radiation potentiates in combination with chemotherapy to increase the risk. Overall, 70% of radiation necrosis is stable or improved. 30% of radiation necrosis are variable on follow-up that may reappear, progress (with re-radiation), or have new distant lesions.

Radiation necrosis has particular patterns of enhancement. There may be new enhancement on initially non-enhancing tumor, distant enhancing foci, periventricular and callosal enhancing foci, and soap bubble or Swiss cheese patterns (Figure 2). Periventricular white matter is one of the most susceptible areas to radiation necrosis [6].

The soap bubble pattern results from diffuse necrosis affecting the white matter and adjacent cortex while the Swiss cheese pattern is typically more diffuse and larger in area [6,8].

It can be challenging to differentiate between radiation necrosis versus reoccurrence of the tumor. Similarities include contrast enhancement, mass effect, and vasogenic edema. However, tumor, not radiation necrosis, has increased relative cerebral blood volume (rCBV). Advanced imaging of radiation necrosis demonstrates low rCBV, no restricted diffusion, and low choline peak on MR spectroscopy. Radiation necrosis tends to be stable or improve over time. Also, if enhancing lesions develop at a distance away from the primary tumor, radiation necrosis should first be suspected [6]. Additionally, combination of corpus callosum involvement

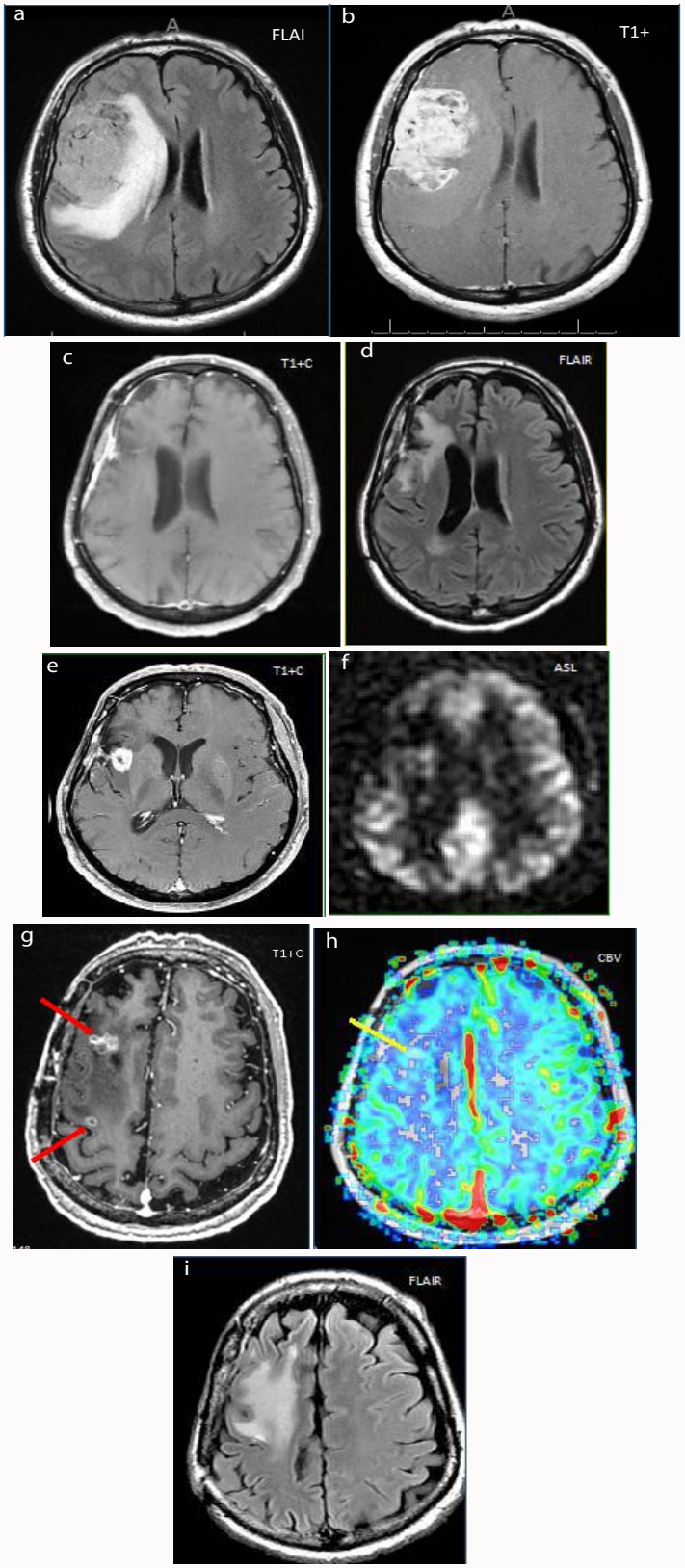

Figure 2a-b: Preoperative MRI shows FLAIR hyperintense and infiltrative GBM with prominent heterogeneous enhancement on post contrast T1Wimages.
Figure 2c-d: 2 years after surgery and completion XRT/TMZ. No significant FLAIR hyperintense or postcontrast T1W enhancement at surgical bed, which indicates absence of significant tumor residue.
Figure 2e-f: 3 years after surgery. New enhancing lesion on T1W postcontrast images, without increased perfusion on ASL;demonstrated to be radiation necrosis on pathology.
Figure 2g-i: 4.5 years after surgery. Newenhancing "soap bubble" distant foci (↑) on enhanced T1W images, not hyper-perfused on dynamic susceptibility contrast perfusion study (↑). Still on surveillance, but thought to be new distant foci of radiation necrosis.

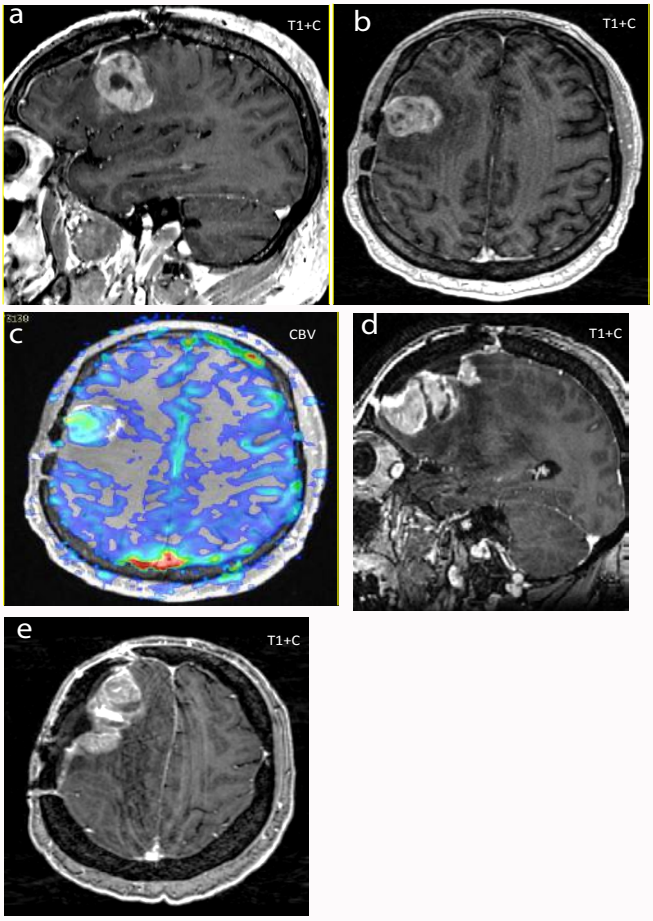

Figure 3a-c: Recurrent enhancing GBM (T1W) 18 months after total resection/XRT (60Gy)/TMZ, (no extra-axial lesions/clean surgical flap), underwent redo GBM resection.
Figure 3d-**e**: Follow up 11 months later, after GBM Resection x 2 + XRT boost (20 Gy) +TMZ, a collision extra-axial T1W enhancing meningioma in the resection-radiation site (at bone flap) is present.

and multiple enhancing lesions +/- crossing the midline and subependymal spread favors tumor progression [9].

Radiation-induced meningioma is the most common central nervous system neoplasm caused by ionizing radiation (Figure 3). Risk increases with increased doses. Even low doses significantly increase the risk of inducing meningioma. Higher proportions of multiple meningiomas and atypical or anaplastic meningiomas are observed in patients who have received radiation therapy compared to those patients who have not. Patients who have received radiation have a lower mean age of presentation, 29 to 38 years for those exposed to high dose radiation compared to 45-58 years in spontaneous cases [10].

Radiation can cause early vascular changes such as increased capillary permeability, vasodilation and delayed injury leading to occlusion/infarction, as well as proliferative changes such as capillary telangiectasia and cavernous malformation. Capillary telangiectasias are thin-walled capillaries with intervening normal brain parenchyma and occur 3-9 months after irradiation. Cavernous malformations do not contain the intervening brain parenchyma and tend to develop years later. Cavernous malformation, on imaging, presents with distinctive "popcorn" appearance with minimal surrounding edema (Figure 4). On CT, there may be ring-like calcifications with core reticulation of variable attenuation. On MR, there may be core heterogeneous signal intensity with dark peripheral hemosiderin rim [11].

Radiation can cause cerebral hemorrhage resulting in the formation of cerebral microbleeds. These microbleeds contain focal perivascular collections of hemosiderin and persist for years [12]. Hemosiderin contains iron and has associated susceptibility effects. MR may show small, round, hypointense lesions on T2*-weighted images obtained using gradient echo or susceptibility-weighted sequences (Figure 5). There is increase in number of lesions over time after irradiation that correlates with dose and target volume. Therefore, monitoring these lesions may be a useful measurement of radiation injury [12].

Chemotherapy imaging-related changes

Traditional chemotherapy primarily induces DNA damage to dividing cells and/or interferes with DNA repair [4]. The addition of temozolomide (TMZ) chemotherapy to radiation therapy was shown to increase mean survival in newly diagnosed glioblastoma from 12.1 to 14.6 months [8]. Following treatment with TMZ, a phenomenon of increased contrast-enhancing lesion size was documented [8] (Figure 6). This was later termedpseudoprogression and is defined by non-tumoral increased enhancement of lesion after treatment seen in approximately 20% of patients treated with concomitant TMZ and radiotherapy [8]. Mechanism of pseudoprogression involves demyelination secondary to hypoxia and endothelial damage, necrosis, and activation of VEGF (due to increase permeability of

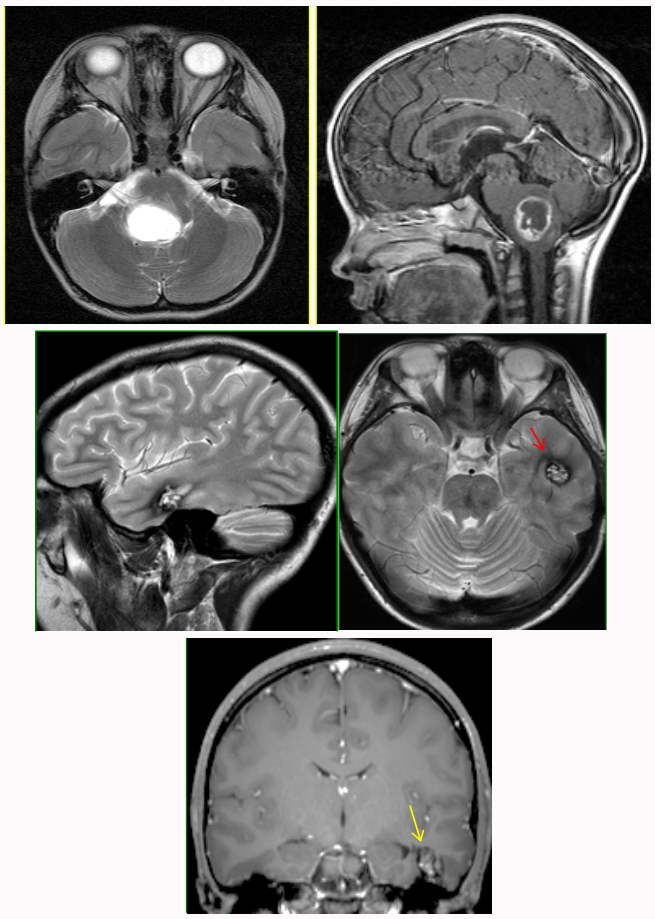

Figure 4a-b: Initial presentation of T2 hyperintense and peripherally enhancing T1W brainstem pilocytic astrocytoma. Received wide-field radiation.
Figure 4c-e: 10 years later: New lesion in the left temporal lobe consistent with cavernous malformation
(↑): Popcorn appearance with surrounding hemosiderin rim on T2
(↑): minimal/no enhancement on postcontrast T1W images.

blood-brain barrier leading to enhancement and vasogenic edema).

Chemotherapy treatments can create difficulty in post-treatment response interpretation. By the Macdonald's criteria, this enhancement may be interpreted as tumor progression using traditional T1-weighted post contrast scans. Hence, Response Assessment in Neuro-oncology (RANO) criteria is an updated methodology for treatment response. RANO uses FLAIR/T2 hyperintensity as a surrogate for non-enhancing tumor. One drawback of RANO is that it can difficult to differentiate between similar appearing FLAIR/T2 hyperintensity such as that caused by radiation-induced gliosis [13]. Much of the current research involves the search for physiologic rather than anatomic techniques to assess tumor response.

MR is unable to directly differentiate between pseudoprogression versus early disease progression except by evaluating changes on follow-up exams [3]. Most cases of pseudoprogression result in spontaneous "remission" in the first 3 months or stability for 6 months. Pseudoprogression is a sub acute change that can occur with or without clinical deterioration, but most patients do not show clinical symptoms despite increased radiologic abnormalities [3]. It is shown that pseudoprogression development actually correlates with better outcome and survival. This may be due to possible anti-tumor inflammatory response and therefore seen as a favorable treatment response [3,8].

Pseudoprogression is more common in patients with (+) methylated status. Methylation of O (6)-methylguanine-DNA methyltransferase (MGMT) promoter leads to low MGMT expression and show more sensitivity to TMZ. There is up to 91% probability of pseudoprogression in patients with methylated MGMT and 59% probability of early true tumor progression in patients without the methylation status [3].This increased sensitivity to TMZ in patients with (+) methylated status is a good indicator of therapeutic response and may indicate a better overall survival.

Therefore, it is important to recognize pseudoprogression as a favorable treatment response. Patient can continue treatment when pseudoprogression is recognized rather than stopping treatment believing that the enhancement is due to early treatment failure. Furthermore, if TMZ is discontinued erroneously, the new treatment strategy may lead to decreased enhancement due to resolution of pseudoprogression with false attribution to the efficacy of the new treatment.

Biological imaging-related changes

Biological therapy can be used as treatments that exploit the immune system to recognize and fight cancer cells. Glioblastoma is associated with increased Vascular Endothelial Growth Factor (VEGF) that results in highly angiogenic tumors with disorganized vessels. The abnormal vessels have decreased vessel permeability with localized hypoxia that induces a cycle of further increase in VEGF [14]. By reducing angiogenesis, it is thought that perhaps the tumor

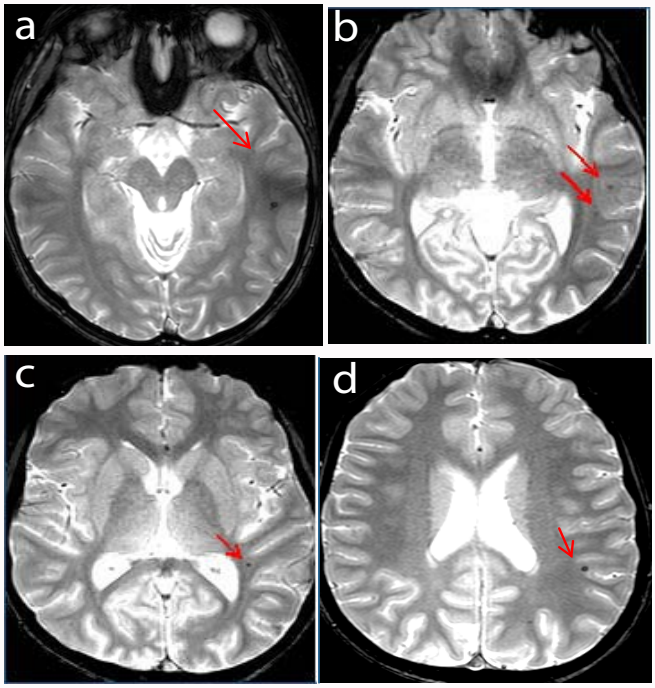

Figure 5a-d: 15 years old status post infratentorial ependymoma resection and radiation 6 years ago. New tiny left temporo-parietal T2 hypointense foci in an otherwise unremarkable supratentorial brain. (↑)

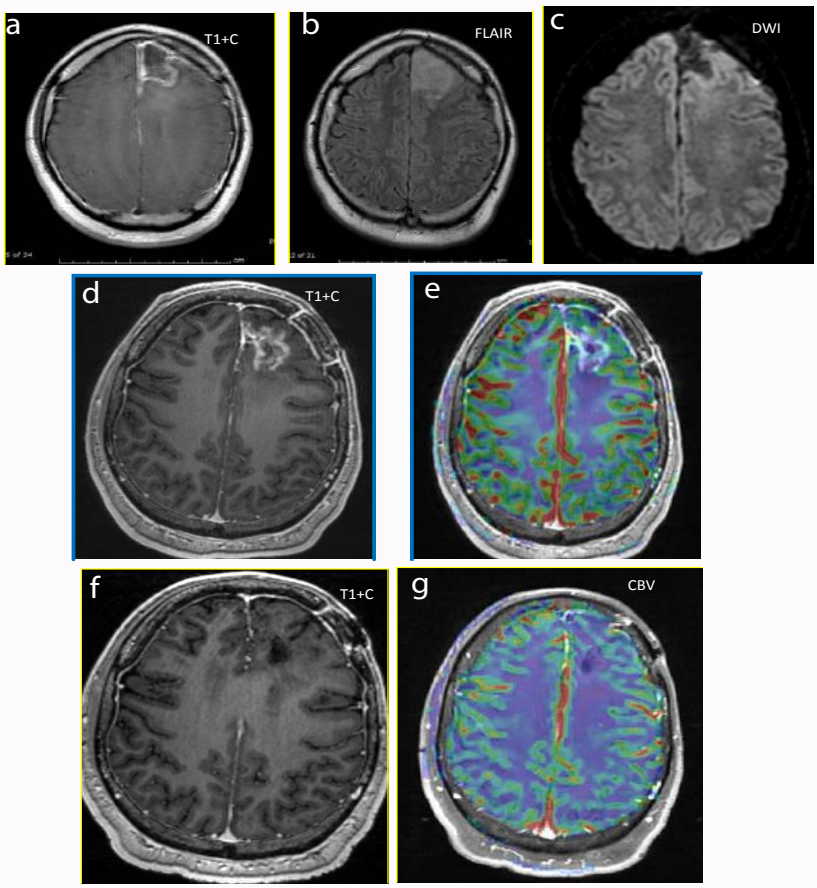

Figure 6a-c: Initial Postoperative images after GBM resection with no significant residue. No nodular enhancement on T1W. No surrounding FLAIR hyperintensity or restricted diffusion.
Figure 6d-e: 3 months after XRT-TMZ, new enhancing lesion on T1W images along the margins of the left frontal resection cavity without increased perfusion (no elevated rCBV).
Figure 6f-g: 9 months after XRT-TMZ, spontaneous resolution of enhancing, non-hyperperfused lesion.

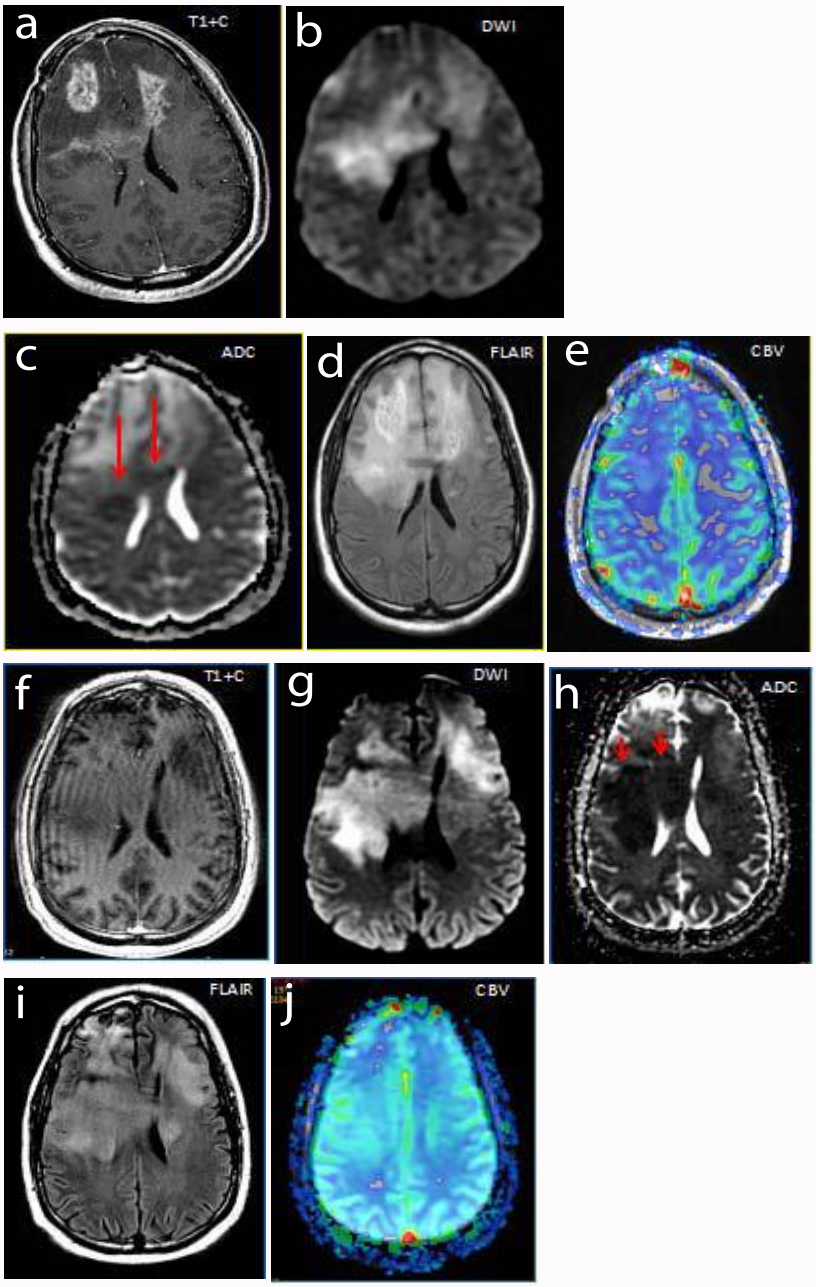

Figure 7a-e: Baseline recurrent bifrontal enhancing glioblastomapostcontrast T1 with, small focal areas of restricted diffusion (↑) on DWI/ADC ,extensive surrounding FLAIR hyperintensityand no significant increased perfusion (rCBV).
Figure 7f-j: 2 months after Bevacizumab, resolution of enhancement on postcontrast T1W, with worsening areas of restricted diffusion (↑) DWI/ADC. Worsening FLAIR hyperintensitywithout significant increase perfusion (rCBV).

would be limited by hypoxia and nutrient deprivation. However, increased hypoxia actually promotes angiogenesis, cancer cell invasion, and possibly treatment resistance [14].

Bevacizumab (BEV) is approved for use in patients with recurrent glioblastoma. BEV inhibits angiogenesis by acting as an antibody that targets VEGF [4]. It is thought that in patients with recurrent glioblastoma, BEV can "normalize" tumor vasculature and blood-brain barrier and has measurable radiographic response. Reduced contrast enhancement can be seen as early as day 1 after start of therapy [14]. Fast reduction in tumor contrast enhancement often occurs within days due to decreased vascular permeability and improved edema [13]. On perfusion imaging, there is also decreased cerebral blood volume due to reduced vessel size [15]. Post-treatment decrease in contrast enhancement and edema may be seen in 25 to 60%of patients, but may not necessarily indicate true tumor reduction [16]. This phenomenon of persistent viable tumor combined with marked decreased in contrast enhancement on edema on MR after starting BEV is termed pseudo response (Figure 7).

Additional explanations for pseudo response include viable hyper cellular tumor, pseudo-infarct/infarct, atypical necrosis, metastasis, gliomatosis phenotype, mix of tumor and treatment effect, and resistance to therapy [14,17]. Eventually, glioblastoma treated with angiogenics such as BEV will progress due to two theories of resistance. Tumors may acquire the ability to evade angiogenic blockade or have

a primary resistance to therapy [14]. Resistance to therapy can be due to vessel co-option, mimicry, hypoxia-induced up regulation of other angiogenic factor, among other mechanisms [14,17]. On the other hand, studies show that BEV may not necessarily promote increased remote risk of malignant glioma relapse [18].

Studies have found that BEV improves symptoms from mass effect and quality of life, but does not improve the overall survival rate [19]. Despite approval for recurrent glioblastoma, BEV may not be beneficial in unselected populations. However, no validated biomarkers exist for patient stratification at this time to help identify the subset of patients most likely to benefit from BEV [14].

Alternative techniques such as diffusion-weighted imaging and restriction-spectrum imaging have shown to be promising in defining tumor response and non-enhancing tumor progression [20,21]. Contrast enhancement is a poor way to monitor tumor response due to permeability of the blood-brain barrier. BEV is noted to cause marked persistent areas of restricted diffusion in patients with highly cellular tumors such as glioblastoma [22]. Therefore, restricted diffusion can be used as a method to monitor treatment response after radiation and chemotherapy [15]. This BEV-associated restricted diffusion is thought to represent a form of radiation necrosis based on pathology [15].

Conclusion

In conclusion, radiation injuries to the central nervous are well documented and can occur within weeks in the form of vasogenic edema but often have additional delayed effects months to years later including leukoencephalopathy, cerebral atrophy, necrosis, induction of neoplasm and vasculopathy. Chemotherapy and biological therapy has been found to complicate the post treatment picture by pseudoprogression and pseudo response. By understanding the typical post-treatment responses seen in MR imaging, better clinical decisions can be made.

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