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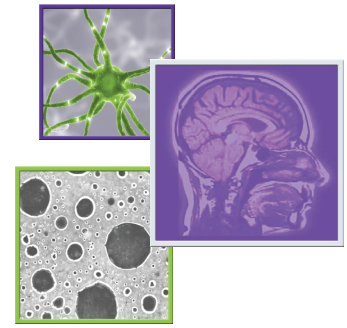

Bevacizumab: radiation combination produces restricted diffusion on brain MRI

John R Hesselink*[,1], Matthew J Barkovich[1], Tyler M Seibert[3], Nikdokht Farid[1], Karra A Muller[2], Kevin T Murphy[3] & Santosh Kesari[4]

Summary points

- VEGF inhibitors, such as bevacizumab (BEV), normalize the blood–brain barrier and reduce capillary permeability, resulting in decreased enhancement and peritumoral edema on imaging.
- Since the tumor cells remain viable, this effect of BEV has been called pseudoresponse.
- Over time, BEV also reduces vessel size, resulting in decreased cerebral blood volume on perfusion imaging.
- Highly cellular tumors, such as glioblastoma (GBM), exhibit restricted diffusion on diffusion-weighted MR imaging, which can be used to monitor treatment response following radiation and chemotherapy.
- Restricted diffusion is also seen in BEV-treated cerebral gliomas in regions of high-dose radiation.
- This diffusion restriction is seen both within the tumor mass and in the peritumoral brain tissue within the radiation field.
- Based on pathology, MR spectroscopy and PET, these areas of BEV-associated restricted diffusion represent a form of radiation necrosis.

SUMMARY **Aims:** The purpose of this paper is to investigate the effect of bevacizumab (BEV) on the diffusion properties of irradiated brain gliomas. **Materials & methods:** Neuroimaging studies and medical records of 44 patients undergoing treatment for cerebral gliomas were reviewed. MRIs were analyzed for presence of restricted diffusion, time to onset, pattern/location, duration of restriction, and persistence of restriction post-treatment with BEV. **Results:** Patchy confluent areas of diffusion restriction on MRI were found in 12 patients. All 12 patients received radiation therapy followed by BEV therapy. Diffusion restriction appeared 3 to 21 months after onset of radiation and 1 to 6 months after starting BEV therapy, increased in size over time, and persisted up to 23 months while on BEV. Restricted diffusion was observed in areas that received 60 Gy or more of radiation. Areas of restricted diffusion showed low T1 and increased T2 signal intensity, minimal or no contrast enhancement, and low cerebral blood volume. A thin perimeter of susceptibility outlined the restricted areas on susceptibility-weighted images in nine patients (75%). Small focal areas of tumor recurrence within larger regions of restricted diffusion were evident in only four patients (33%). In seven patients (58%) the area of restricted diffusion showed necrosis or radiation change on histology or no metabolic activity on MR spectroscopy or PET. **Conclusion:** Restricted diffusion associated with BEV-treated cerebral gliomas occurs in regions of high-dose radiation and does not indicate high-cellularity of tumor recurrence.

KEYWORDS
• bevacizumab • cerebral glioma • restricted diffusion • MRI

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Background

Gliomas are the most common malignant primary neoplasms of the brain. Standard treatment is surgery, followed by radiation therapy and adjuvant chemotherapy. High-grade gliomas, especially glioblastomas (GBM), are very vascular tumors with a high degree of VEGF expression. BEV, a monoclonal antibody targeted against VEGF, is often added to the treatment regimens of high-grade gliomas to suppress VEGF activity [1]. As a result of normalization of the damaged blood–brain barrier and reducing tumor vascularity, VEGF inhibitors decrease tumor enhancement and peritumoral vasogenic edema [2,3]. Restricted diffusion has been reported in malignant glioma patients receiving BEV [3–7]. On routine clinical reads, we also noticed prominent and often large areas of restricted diffusion in BEV-treated patients that did not seem to correlate with tumor recurrence. The purpose of this project was to investigate the features of this restricted diffusion and to search for clues about causation.

Materials & methods

• Patients

Imaging studies and medical records of 44 patients treated with radiation plus adjuvant chemotherapy for cerebral gliomas were reviewed to evaluate diffusion restriction on post-treatment MRI. Restricted diffusion, defined by high signal on diffusion-weighted imaging (DWI) and low signal on apparent diffusion coefficient (ADC) images, was observed in 14 of 44 patients. Twelve of the patients (seven males and five female), who received BEV at some time during their treatment course, were included in our study group. One patient was enrolled in a blinded multicenter RTOG avastin trial and was excluded from our study because we did not know if the patient received BEV or placebo. One other patient was excluded because we were unable to receive treatment records from an outside hospital. MR scans obtained within 8 weeks after surgical resection were excluded to avoid confusion with post-operative hemorrhage and ischemia. Serial MR scans were obtained at 2- to 3-month intervals. MRIs were analyzed for presence and size of restricted diffusion, time to onset, pattern/location, duration of restriction, and persistence of restriction post-treatment with BEV.

• MRI

MRI was performed on a 3T Signa Excite HDx scanner (GE Healthcare, WI, USA) equipped with an eight-channel head coil. Our imaging protocol included pre- and post-gadolinium 3D volumetric T1-weighted inversion recovery spoiled gradient-recalled sequences (TE/TR = 2.8/6.5 ms; TI = 450 ms; flip angle = 8°; FOV = 24 cm; matrix = 0.93 × 0.93 × 1.2 mm), a 3D T2-weighted FLAIR sequence (TE/TR = 126/6000 ms; TI = 1863 ms; FOV = 24 cm; matrix = 0.93 × 0.93 × 1.2 mm), axial T2-weighted fast spin-echo sequence (TE/TR = 81/3767 ms; FOV = 24 cm; section thickness = 4 mm; matrix = 512 × 384), 3D SWAN (susceptibility weighted imaging [SWI]) sequence (TE/TR = 24.7/42.1 ms; flip angle = 15°; echo train length = 7; section thickness = 3 mm; slice spacing = 1.5 mm; FOV = 22 cm; matrix = 320 × 224), and a spin-echo EPI (echo-planar imaging) DWI sequence (TE/TR = 92/9500 ms; FOV = 28 cm; section thickness = 4 mm; matrix = 128 × 192). ADC images were calculated from acquired DWI data with b = 1000 s/mm^2 and b = 0 s/mm^2. The ADC values were obtained with the largest ROI that would fit within the area of restricted diffusion and compared with an ROI within white matter most distant from the radiation site, which was usually the forceps minor or major in the opposite hemisphere.

• MR spectroscopy

Multivoxel proton spectra were obtained using point-resolved spectroscopy (PRESS) with a TR 1000 msec, TE 144 msec, FOV 20 cm, matrix 16 × 16, and NEX 1 in the axial plane. Frequency domain peaks of NAA (*N*-acetylaspartate, 2.0 ppm), creatine (3.0 ppm) and choline (3.2 ppm) were evaluated in all spectra. The relative quantity of choline was measured as the ratio of its peak height to creatine and NAA. Spectra were considered abnormal if the peak height of choline was >1.2 or 1.5 greater than NAA and creatine, respectively.

• PET-CT

^{18}F FDG PET CT was obtained in patients with clinical suspicion of tumor recurrence and equivocal appearance on MRI and MR spectroscopy. Imaging was performed on a GE Discovery VCT PET/CT (15.7 cm axial field of view, 70 cm transaxial field of view, 4.7 × 6.3 × 3.27 mm cross-slice resolution, 3.27 mm interslice distance). All patients were asked to fast for at least 6 h prior to their scan. Blood glucose levels were measured before the FDG injection. Following

injection of 370 MBq (10 mCi) FDG intravenously, a 30 frame dynamic image acquisition was obtained over 60 min.

Results

Restricted diffusion was seen in 14 patients. Two of those patients were excluded from our study group because of incomplete clinical data. Of the 30 patients who did not receive BEV, focal intratumoral areas of restricted diffusion were seen in only two patients (7%), but the restricted areas were less than 1 cc in size.

All 12 patients (100%) in the BEV-treated group showed patchy confluent volumes (5–75 cc, mean 28 cc) of diffusion restriction on brain MRI. Mean ADC values were 541 × 10^{-6} mm^2/s for areas of restricted diffusion (range: 403 to 686 × 10^{-6} mm^2/s), compared with 703 × 10^{-6} mm^2/s (range: 625 to 749 × 10^{-6} mm^2/s) for normal appearing white matter. Tumor histology included ten GBMs, one anaplastic glioneuronal tumor and one gemistocytic astrocytoma (Table 1). Ages ranged from 36 to 65 years (mean = 50 years). All patients received radiation therapy (60–66 Gy in 30 fractions) followed by BEV therapy (10 mg/kg every 14 days). Adjuvant chemotherapy is shown in Table 1. Diffusion restriction appeared 3 to 21 months after onset of radiation treatment and 1 to 6 months after starting BEV therapy, increased in size over time, and persisted up to 23 months while on BEV (Figures 1 & 2). The restricted diffusion persisted up to 4 months after BEV was stopped. No data beyond 4 months was available. Restricted diffusion occurred both within and outside the pre-treatment margins of tumor enhancement. Radiation isodose curves were available in eight patients, and restricted diffusion was observed in areas that received 60 Gy or more of radiation (Figure 1C). Areas of restricted diffusion showed low T1 and heterogeneous increased T2 signal intensity, minimal or no contrast enhancement, and low cerebral blood volume on perfusion MRI. A subtle rim of enhancement was visible in six patients (50%) (Figures 1H & 2K), but one of them had been off BEV for several months.

A thin perimeter of susceptibility outlined the restricted areas on SWI images in nine patients (75%) (Figure 1F). In the three patients without a perimeter of susceptibility, the areas of restricted diffusion were smaller and in regions of tumor necrosis. In five patients, the perimeter of susceptibility appeared at the same time as the restricted diffusion. The perimeter of susceptibility was visible within 1–4 months in the other four patients. In one patient, an autopsy of the brain showed eosinophilic coagulative necrosis corresponding to the area of restricted diffusion (Figure 1). The histologic correlate of the radiologic perimeter of susceptibility was a band of reactive gliosis separating central necrosis from neocortex. This gliosis was characterized by white matter vacuolization and many plump,

Table 1. Timing of restricted diffusion with bevacizumab therapy.

Case	Age/sex	Pathology	Adjuvant therapy	Restricted diffusion (months)			
				Time from XRT start	*Time from BEV start*	*Progression on BEV*	*Persistent after BEV stopped*
1	53/M	GBM	TMZ, nilotinib	3	3	17	No data
2	51/M	Gemistocytic astrocytoma, grade 2	TMZ, erlotinib	7	2	18	2
3	44/M	Anaplastic glioneural tumor, grade 3	TMZ	10	2	4	2
4	36/F	GBM	TMZ	21	1	No data	No data
5	62/F	GBM	TMZ	16	2	7	No data
6	57/F	GBM	TMZ	9	3	4	No data
7	57/M	GBM	TMZ	5	2	5	No data
8	43/M	GBM	TMZ	8	1	7	3
9	41/M	GBM	TMZ	12	6	18	No data
10	48/F	GBM	TMZ, dasatinib	8	3	3	No data
11	65/M	GBM	TMZ	5	3	5	4
12	43/F	GBM	Erlotinib, rapamycin	5	3	23	No data

All patients received radiation (60 Gy in 30 fractions plus) and were on BEV, 10 mg/kg every (q) 14 days. Dasatinib dose was 100 mg daily. Erlotinib dose was 600–1200 mg q 4–6 days. Rapamycin dose was 10 mg q 10 days.

BEV: Bevacizumab; F: Female; GBM: Glioblastoma; M: Male; TMZ: Temozolomide, 150–300 mg q 5 days; XRT: Radiation treatment.

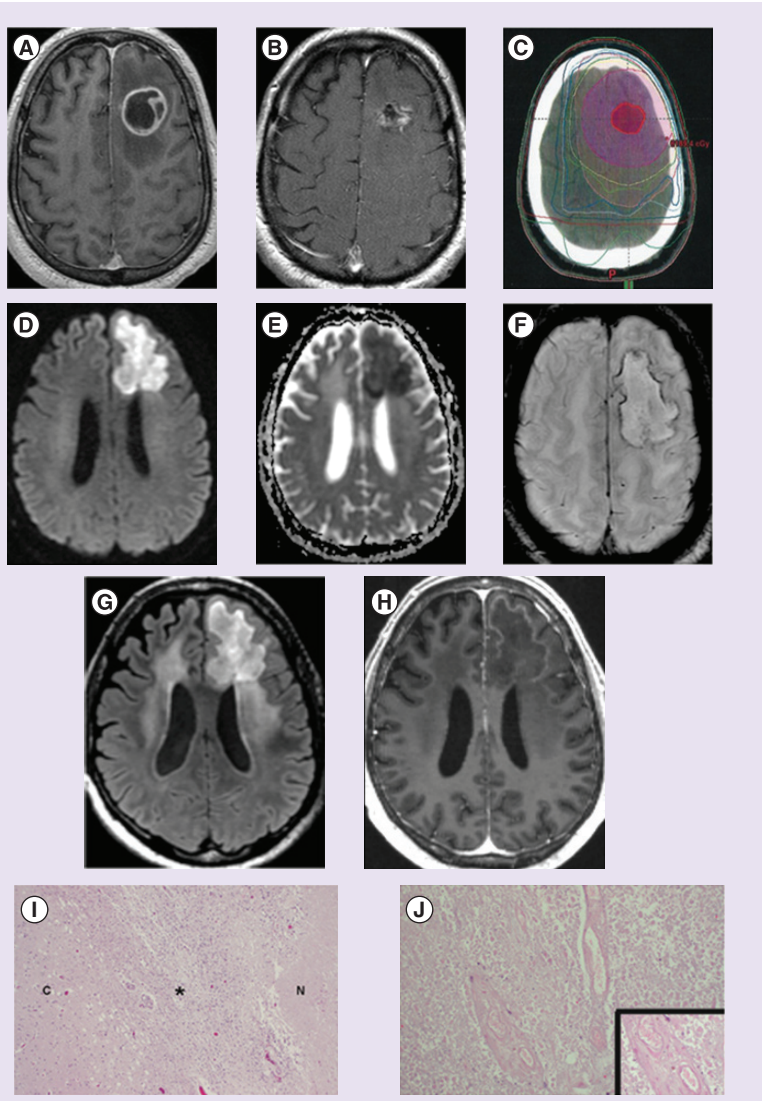

Figure 1. Case 1: a 53-year-old man with glioblastoma. (A) T1 post-contrast MRI shows a ring-enhancing mass in the left frontal lobe with surrounding vasogenic edema. **(B)** A postoperative T1 post-contrast scan shows complete resection of the mass. Patient was treated with radiation and adjuvant temozolomide and bevacizumab. **(C)** On the radiation dose map, the left frontal lobe received 62 Gy or more of radiation. **(D, E)** After 15 months of bevacizumab therapy, diffusion-weighted imaging and apparent diffusion coefficient images reveal a large area of restricted diffusion in the left frontal lobe surrounding the original site of enhancing tumor. **(F)** Susceptibility-weighted imaging shows a thin perimeter of susceptibility outlining the restricted region. **(G)** On a fluid attenuation inversion recovery (FLAIR) image, the restricted area is hyperintense and slightly higher signal than adjacent white matter edema and gliosis. **(H)** A T1 post-contrast image reveals only a thin perimeter of enhancement. **(I)** Micrograph of brain autopsy tissue from the perimeter of the left frontal lobe lesion showing cortex (represented by the letter C) and necrosis (represented by the letter N) separated by a thin band of white matter gliosis (*); 40× magnification. **(J)** Higher-power view of eosinophilic coagulative necrosis from the center of the left frontal lobe lesion; 200× and 400× (inset) magnification. Both images are from hematoxylin and eosin-stained tissue.

reactive gemistocytes. Scattered hemosiderin-laden macrophages were also seen within this area, suggestive of prior hemorrhage.

Tumor progression over time was confirmed in 11 patients (92%) by MR spectroscopy (seven cases), PET (eight cases), biopsy (two cases) and autopsy (four cases). Tumor recurrence within areas of restricted diffusion was evident in only four patients (33%). In eight patients (66%), the area of restricted diffusion showed necrosis or radiation change on histology, or no metabolic activity on MR spectroscopy or PET.

Two of the 12 patients (16%) showed small focal areas (less than 1 cc) of restricted diffusion within the tumors before treatment, but the areas of restricted diffusion following BEV therapy were much larger and more confluent.

Discussion

Bevacizumab, an anti-VEGF monoclonal antibody, has been added to the treatment regimen for high-grade gliomas, especially GBMs. By inhibiting VEGF, BEV prevents GBMs from inducing additional vascular supply to facilitate rapid tumor growth. One of the first effects of BEV is normalization of the blood–brain barrier and reduced capillary permeability [2,3,8]. This can be seen within a few hours of starting treatment and is reflected on imaging as markedly decreased enhancement and peritumoral edema. Although the tumor reduction can appear quite profound on the images, the tumor cells remain viable, and this has been called pseudoresponse [9]. Over time, BEV also reduces vessel size and tumor blood volume, which can be detected on perfusion imaging [2].

Diffusion-weighted imaging (DWI), which is independent of contrast enhancement, has been proposed as a way to distinguish pseudoresponse from tumor recurrence [10]. If a higher percentage of the free water protons are intracellular, they are likely to be in a more restricted environment. Apparent diffusion coefficient (ADC) values have been shown to correlate with tumor cellularity [11], and ADC can distinguish high-grade from low-grade gliomas [12]. Also, ADC has been used as a marker for tumor progression, including in patients on anti-VEGF agents [10].

However, it is unlikely that increased tumor cellularity accounts for the restricted diffusion that we observed in our patient group. Although malignant and highly cellular, on histology GBMs do not have the dense cell packing like a lymphoma or medulloblastoma, and restricted

diffusion is not a prominent feature of untreated GBMs. Moreover, BEV inhibits VEGF and produces a more ischemic environment, forcing gliomas to co-opt normal blood vessels. As a result, the infiltrating pattern of recurrent gliomas is in a more perivascular distribution with overall less cellularity compared with the original parent tumor [5]. Increased ADC values and ADC ratios were previously observed in brain tumors [13], and higher ADC values before the start of BEV have been shown to be predictive of longer progression-free survival [14]. However, ADC values of recurrent glioma were higher than those of radiation necrosis [15].

The molecular environment of high-grade gliomas is heterogeneous. Increased ADC due to edema and necrosis will offset the reduced ADC of increased cellularity, resulting in ADC values similar to normal brain. White *et al.* [16] have proposed restriction spectrum imaging (RSI), a DWI technique that can separate the hindered and restricted water compartments in tissues. With this technique, they can select out the intracellular restricted components and present the data as 'RSI cellularity maps'.

Restricted diffusion can be present within high-grade gliomas both before and after radiation and chemotherapy, likely due to areas of ischemia where the tumor outgrows its blood supply. This restricted diffusion tends to be focal and scattered throughout the mass, quite unlike the larger patchy and contiguous regions of restricted diffusion we observed with BEV (Figures 1 & 2). In our series, diffusion restriction was seen both within the tumor mass and peritumoral brain tissue within the radiation field. In eight of 12 patients (66%) the area of restricted diffusion showed necrosis or radiation change on histology or no metabolic activity on MR spectroscopy or PET. In the other four patients (33%) with tumor recurrence, the areas of restricted diffusion likely consisted of a mixture of tumor and radiation necrosis, but predominantly radiation necrosis.

Mong *et al.* [7] reported relative stability of the restricted-diffusion lesions, with little change in ADC values or volume of the lesions for up to 6 months. In our series, six out of 12 patients (50%) showed progressive increase in volume of the restricted diffusion over 2–23 months (Figure 2).

Additionally, several authors reported that the diffusion restriction clustered around the lateral ventricles and in the corpus callosum [7,17]. We noted that pattern in only three of 12 cases (33%) (Figure 2). The location of restricted diffusion depended more on the original site of tumor and the regions of the brain receiving 60 Gy or more of radiation.

The restricted diffusion in BEV-treated patients is unlikely to be ischemic in nature. The reduced ADC in ischemia and infarction usually resolves after 1 week. The restricted diffusion in our patients persisted for up to 23 months while on BEV. A chronic ongoing ischemia is unlikely since we did not observe any increased lactate on MR spectroscopy in any of the patients. Finally, the persistence of the restricted diffusion suggests a more chronic, static condition, such as radiation

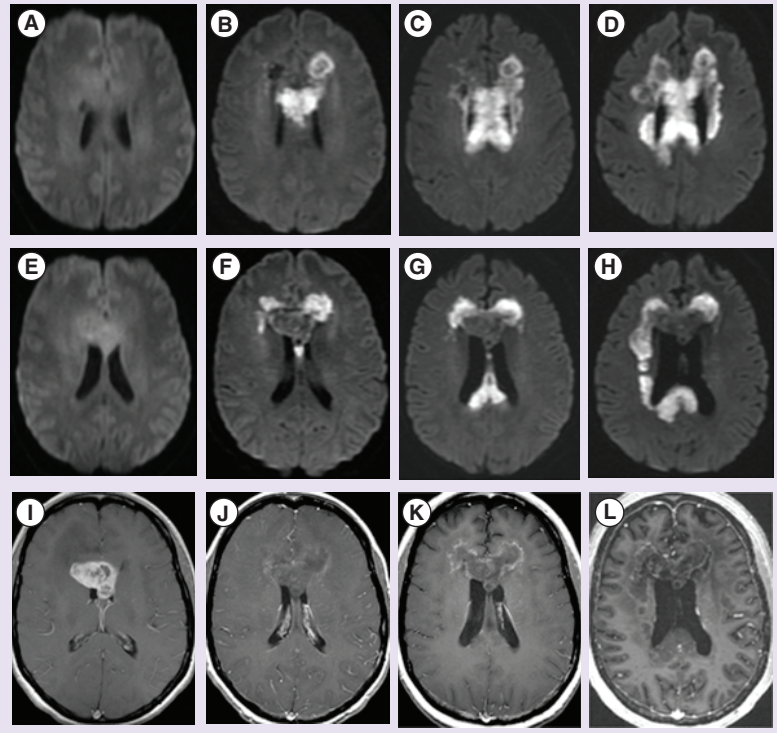

Figure 2. Case 12: a 45-year-old woman with a glioblastoma. The original tumor centered in the anterior corpus callosum was treated with 66 Gy of radiation. The posterior corpus callosum was in the 35 Gy isodose region. When a follow up MRI 3 months later showed new satellite lesions in the left frontal lobe and posterior corpus callosum, those areas were given a boost of 24 Gy. Diffusion-weighted imaging **(A–H)** and T1 post-contrast images **(I–L)** at baseline (first column), 5 months (second column), 12 months (third column), and 26 months (fourth column) after radiation and adjuvant bevacizumab show progressive restricted diffusion in the corpus callosum and periventricular white matter. Note that the original enhancing tumor did not exhibit restricted diffusion. T1 post-contrast images (bottom row) demonstrate suppressed enhancement while on bevacizumab. PET was negative for recurrent tumor.

necrosis, and the available histology in selected patients revealed hypocellularity, gliosis, coagulative necrosis and radiation change such as white matter vacuolization.

The pattern of abnormality that we observed is also very different than traditional radiation necrosis that typically occurs 18–24 months post treatment and on imaging appears as an enhancing mass with a central area of necrosis [18]. An autopsy in Case 1 showed eosinophilic coagulative radiation necrosis in the area of restricted diffusion (Figure 1). The cortex was relatively spared. Vessels throughout the lesional area were thickened and hyalinized. The white matter also showed foci of vacuolization, consistent with radiation change. Mong *et al.* [7] also reported prominent perivascular fibrosis and diffuse necrotic changes. The surgical description of their case was 'gelatinous necrotic tissue'.

What are the histological/microstructural correlates of restricted diffusion in patients receiving radiation followed by BEV therapy? The water molecules are likely in a noncellular restricted environment. Any physical barriers can restrict molecular motion, such as gliosis or cellular and axonal remnants of radiation necrosis. The water protons could be in a more desiccated environment with elevated protein and increased viscosity. Normalization of the blood–brain barrier and decreased vascular permeability induced by BEV may decrease extracellular water content and narrow the extracellular space in relation to the cellular and microvascular compartments [3]. Less water molecules in compacted compartments will give more signal on DWI sequences than large quantities of water in a freely diffusible medium. We looked at the T1 and T2 signal intensities within the restricted diffusion and compared them to peritumoral edema. Although the T1 and T2 tended to be higher and lower, respectively, in the areas of restricted diffusion, the results were inconsistent. It is also difficult to derive a measure of the size of the water compartments by pathological examination because the water is removed with the fixation process and retraction occurs. Electron microscopy could be pursued to look for physical barriers in the restricted lesions.

One interesting finding that we noted in nine patients (75%) was a distinct thin line of susceptibility surrounding the areas of restricted diffusion on SWI images (Figure 1F). This perimeter of susceptibility is not unique to BEV-associated necrosis. It has been thought to represent accumulations of macrophages, glial cells and microglia around necrotic tissue. This was confirmed histologically in one case at the time of autopsy. The cortex was separated from coagulative necrosis (representing the restricted diffusion) by a rim of reactive gliosis. This gliosis contained reactive gemistocytes (astrocytes), vacuolated white matter, and scattered macrophages, including some with hemosiderin. The hemosiderin-laden macrophages were evidence of a prior hemorrhage in that location. No tumor cells or calcium were seen. This perimeter of susceptibility may be a helpful sign to distinguish BEV associated necrosis with restricted diffusion from recurrent tumor.

As mentioned above, BEV therapy has been associated with pseudoresponse due to the reduced enhancement and peritumoral edema. Now it is apparent that BEV can also produce a pattern of pseudoprogression in the form of restricted diffusion. Observing progressively enlarging areas of restricted diffusion on serial MR images can appear quite alarming, and when first encountered, both neuroradiologists and neuro-oncologists were interpreting it as tumor progression. This restricted diffusion is different than the pseudoprogression observed within the first 6 months of radiation because the latter exhibits increased enhancement and edema that fades over time [19]. The restricted diffusion we observed started 3–21 months after radiation and continued to increase up to 23 months.

Our study has several limitations. First, it was a retrospective study and our numbers are relatively small (12 cases). We had no control over variables of therapy. The radiation dose of 60 Gy and the BEV doses were quite consistent, but the time from radiation to start of BEV treatment was variable. All but one patient received adjuvant temozolomide, but the dosage varied depending on tumor response and patient tolerance of the drug. As far as we know, temozolomide has no effect on the observed diffusion restriction. Four patients also received other chemotherapeutic agents. As discussed above, the four autopsies provided valuable information, but the surgical biopsies were limited and were not always taken from the areas of restricted diffusion. Cross-referencing the biopsy sites with specific locations on the images was problematic. More targeted biopsies coordinated with the imaging findings would be helpful for future investigations.

Conclusion

Restricted diffusion associated with BEV-treated cerebral gliomas occurs in regions of high-dose

radiation and does not indicate high-cellularity of tumor recurrence or chronic ongoing ischemia. Diffusion restriction is seen both within the tumor mass and in the peritumoral brain tissue within the radiation field. Based on pathology, MR spectroscopy, and PET, these areas of restricted diffusion represent a form of radiation necrosis.

Future perspective

Undoubtedly, new therapeutic agents will continue to be added to the armamentarium of the neuro-oncologist, and these agents may alter the appearance of tumors and normal brain on radiologic images. It is important for the interpreting physician to be aware of the patient's treatment regimen to avoid interpretation errors and to be alert for potential effects of the therapy on the images.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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