Differentiation between glioma and radiation necrosis using molecular imaging of endogenous proteins and peptides

J. Zhou[1], E. Tryggestad[2], Z. Wen[1], B. Lal[3], T. Zhou[1], R. Grossman[4], K. Yan[1], S. Wang[1], D-X. Fu[5], E. Ford[2], J. Laterra[3], and P. C. van Zijl[1]
[1]Department of Radiology, Johns Hopkins University, Baltimore, Maryland, United States, [2]Department of Radiation Oncology, Johns Hopkins University, Baltimore, Maryland, United States, [3]Department of Neurology, Kennedy Krieger Institute, Baltimore, Maryland, United States, [4]Department of Neurosurgery, Johns Hopkins University, Baltimore, Maryland, United States, [5]Department of Oncology, Johns Hopkins University, Baltimore, Maryland, United States

Introduction

Distinguishing tumor recurrence from radiation necrosis, a well-known late radiation injury, has been a diagnostic dilemma in the management of patients with brain tumors for several decades (1). The problem is that treatment-induced injury mimics tumor recurrence both clinically and radiographically, including occurrence of T_2 abnormality, gadolinium enhancement, and mass effect. As anti-tumor therapies are intensified to better control malignancy, the associated risk for brain injury also increases, which represents a major diagnostic challenge in neuro-oncology (2). Currently, there is no reliable imaging modality available for differentiating tumor recurrence from radiation injury. Amide proton transfer (APT) imaging is a new non-invasive MRI technique that detects the amide protons of endogenous mobile proteins and peptides in tissue (3). Recent data suggest that increased APT signal in malignant tumors potentially provides unique information about the presence and grade of brain tumors (4), based on increased cellular content of proteins and peptides. Here, we show that amide protons are a biomarker for tumor presence that can distinguish between tumor and radiation necrosis in animal models.

Materials and Methods

Six adult rats were irradiated using a home-made small animal radiation research platform (single dose, 40 Gy; 10×10 mm^2 on left hemisphere). Twelve nude rats were anesthetized, and human SF188/V+ glioma cells (3×10^6 or 5×10^6 in 4 µl) were stereotactically implanted into the left parietal lobe. APT images (intensity S_{sat}) were acquired at 4.7T using labeling offsets of ±3.5 ppm with respect to water (TR/TE 10s/30 ms; saturation power/time 1.3µT/4 s; slice thickness = 1.5 mm; NA = 16). A control image (S_0) in the absence of radiofrequency saturation was acquired for signal normalization. APT images were quantified using magnetization transfer-ratio asymmetry: $MTR_{asym}(3.5ppm) = 100\%\times[S_{sat}(-3.5ppm) - S_{sat}(3.5ppm)]/S_0$, and displayed using a window of -10% to 10%.

Results and Discussion

Radiation necrosis and glioma show similar features on conventional MR images. Fig. 1(left) shows typical MR images for a rat with radiation necrosis in the left hemisphere, which appeared at about six months post-radiation. We clearly observed a large necrotic lesion that had high gadolinium enhancement. Similarly, a rat with a SF188/V+ brain tumor (Fig. 1, right) showed high gadolinium enhancement.

Radiation necrosis and glioma can be differentiated by APT imaging. In the case of radiation necrosis (Fig. 1, left), APT MRI was hypointense to isointense in the injured areas (as identified by gadolinium enhancement) with respect to the contralateral brain areas. There were dark necrotic cores with the hypointense APT signals. These necrotic cores corresponded well to the centers of the gadolinium-enhancing regions. APT was isointense in the necrotic periphery. Histological brain sections revealed the characteristics of necrosis, namely, parenchymal coagulative necrosis with sporadic bleeding. High-magnification histology clearly showed the presence of necrotic cells and damaged vessels, which was most apparent in the cores of necrosis. In contrast, the SF188/V+ tumor xenografts (Fig. 1, right) showed APT hyperintensities in the most viable, actively growing tumor areas, as identified by gadolinium enhancement and histology. The APT hyperintensity was a unique feature of these tumors, suggesting a higher mobile protein and peptide concentration in gliomas, as revealed by MRI-guided proteomics (5). The coronal histological sections clearly showed the tumor masses, which consisted of dense tumor cells.

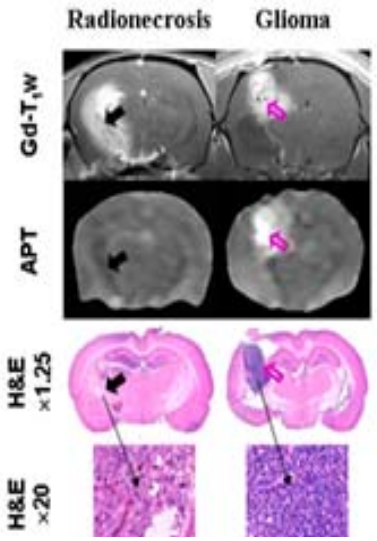

Fig. 1. MR images and histology of radiation necrosis and glioma

Quantitative Analysis. In the radiation-injured brain, the average APT intensity was -3.4% ± 0.3% (n = 6) in the gadolinium-enhancing necrotic cores and -2.9% ± 0.4% in the contralateral brain areas (Fig. 2), which was not significantly different (P > 0.1). On the other hand, the average APT imaging intensity in the tumor group was 12.2% ± 4.6% (n = 12), significantly higher than in contralateral brain (-1.5% ± 0.6%, P < 0.001). The average APT contrast between the tumor and contralateral brain tissue was 13.7%, with a 95% confidence interval of 10.2% to 17.2%.

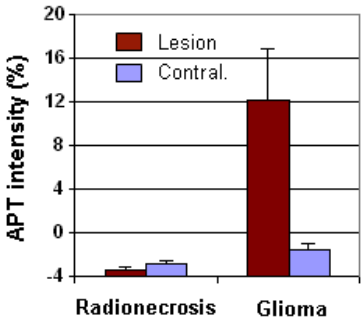

Fig. 2. APT imaging intensities of radiation necrosis and glioma

Conclusions

Radiation necrosis and gliomas demonstrated markedly different visual appearance on APT MRI, namely, hypointense to iso-intense with respect to contralateral in radiation necrosis versus hyperintense in tumor. The results clearly show that the amide protons detected by APT constitute an imaging biomarker for the presence of the tumor, which can be used to distinguish between active tumors and treatment-induced injury, such as radiation necrosis.

References: (1) Burger et al. J. Neurosurg. 58(1983)159. (2) Yang & Aghi, Nature Rev. Clin. Oncol. 2009; (3) Zhou et al. Nat. Med. 9(2003)1085. (4) Zhou et al. MRM 60(2008)842; (5) Hobbs et al. JMRI 18(2003)530.