Combined Iron Oxide Nanoparticle and Gadolinium Contrast Enhanced MRI Specifically Characterizes Glioblastoma Neuroinflammation Mediated Pseudoprogression

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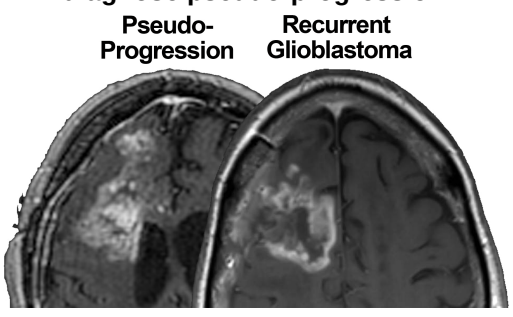
Learning Objectives

-Discuss the role of iron (Fe-) and gadolinium (Gd-) enhanced MRI in the diagnosis of glioblastoma pseudoprogression (Psp).
-Discuss the hypothesized pathophysiology of Fe-enhancement on T1-weighted MRI.

Introduction

Noninvasively differentiating therapy-induced Psp from recurrent disease in patients with glioblastoma is prospectively difficult due to the current lack of a biologically specific imaging metric (**Figure 1**) (1-2). Ferumoxytol iron oxide nanoparticle MRI contrast agents characterize innate immunity mediated neuroinflammation (3-5); therefore, we hypothesized that combined Fe- and Gd-enhanced MRI could serve as a biomarker of glioblastoma Psp.

Figure 1: Gd-MRI does not specifically diagnose pseudo-progression.

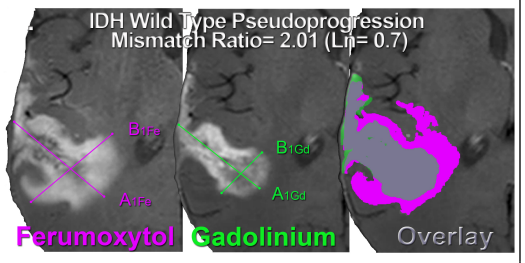


T1-weighted Gd-MRI from two patients with treated glioblastoma demonstrates remarkable similar appearing enhancement in both pseudo-progression (left) and recurrent disease (right). Gd-enhancement represents contrast leakage into the brain interstitial space and is not biologically specific for localizing sites of therapy mediated neuroinflammation.

Methods

Materials and Methods: In this institutional review board approved, retrospective study, we analyzed ferumoxytol and gadolinium contrast enhanced T1-weighted 3T MRI in patients with glioblastoma over multiple clinical time points. IDH-1 mutational status was characterized by exome sequencing. Sum of products diameter measurements were calculated according to RANO criteria from both gadolinium and ferumoxytol enhanced sequences. Enhancement mismatch was calculated as the natural log of the ferumoxytol to gadolinium sum of products diameter ratio (**Figure 2**) (2). Students T-test assessed differences in mismatch ratios. P-value < 0.05 indicated statistical significance.

Figure 2: Sum of Products Diameter Measurements on Fe- and Gd-enhanced MRI



24 hour delayed phase Fe- (left) and Gd-enhancement (middle) mismatch ratio is increased in CRT-mediated pseudo-progression. The sum of products diameter (SPD) was calculated per RANO criteria. Fused enhancement overlay (Fe, pink; Gd, green; overlap, grey; right image) shows the degree of mismatch.

Results

Results: With the development of Psp we observed a significantly elevated mismatch ratio when compared to disease progression (P< 0.01) within IDH-1 wild type patients (**Figure 3**). Patients with IDH-1 mutation demonstrated significantly reduced mismatch ratio with the development of Psp when compared to disease progression (P< 0.01). Receiver operator curve analysis demonstrated 100% sensitivity and specificity for the use of mismatch ratios as a diagnostic biomarker of pseudoprogression. Image guided tissue sampling sites from IDH-1 wild type glioblastoma disease recurrence were categorized by the presence of ferumoxytol or gadolinium enhancement. Ferumoxytol only enhancement demonstrated activated microglia or vascular hyalinization with scattered macrophages in the absence of viable tumor. Dual enhancing sites demonstrated highly cellular tumor with microvascular proliferation and epithelioid TAM.

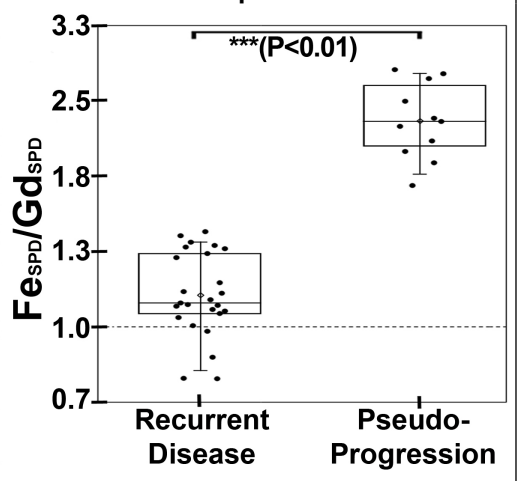
Conclusions

Conclusion: We demonstrate that contrast mismatch ratios are a specific MRI biomarker for the diagnosis of Psp in patients with glioblastoma that may be due to the unique characterization of therapy-induced neuroinflammation.

References

1. Gerstner ER, McNamara MB, Norden AD, et al. Effect of adding temozolomide to radiation therapy on the incidence of pseudo-progression. J Neurooncol. 2009;94(1):97–101.
2. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010 Apr 10;28(11):1963-72.
3. McConnell HL, Schwartz DL, Richardson BE, et al. Ferumoxytol nanoparticle uptake in brain during acute neuroinflammation is cell-specific. Nanomedicine. 2016 Aug;12(6):1535-42.
4. Toth GB, Varallyay CG, Horvath A, et al. Current and potential imaging applications of ferumoxytol for magnetic resonance imaging. Kidney Int. 2017 Apr 14. pii: S0085-2538(17)30119-9.
5. Neuwelt A, Sidhu N, Hu CA. Iron-based superparamagnetic nanoparticle contrast agents for MRI of infection and inflammation. AJR Am J Roentgenol. 2015 Mar;204(3).

Figure 3: Dual Contrast MRI Differentiates Psp from Recurrence.



Graph of mean values by disease status in IDH-1 wild type glioblastoma shows mismatch ratios are significantly different.