Signal loss in DCE-MRI associated with tumor progression in prostate cancer bone metastasis model

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Introduction

Metastases of prostate cancer are commonly found in the bone and are often resistant to conventional chemotherapy. Combined therapeutic approaches targeting both tumor cells and cells in the stroma (endothelial cells, pericytes and fibrolasts) can produce substantial therapeutic effects. Blockade of the phosphorylation of PDGF-Rβ (by STI571) was shown to sensitize endothelial cells in the tumor stroma to a cytotoxic drug (paclitaxel), resulting in apoptosis of endothelial cells leading to improved therapeutic response in an experimental model (1, 2). In another study PDGF-R antagonists induced a decrease in tumor interstitial hypertension thereby increasing trans-capillary transport and effectiveness of chemotherapy (3). The goal of this study is to evaluate the ability of dynamic contrast enhanced (DCE)-MRI to monitor vascular and stromal effects associated with progression and regression of prostate cancer-bone metastases.

Methods

Tumor model: Prostate cancer bone metastasis model was initiated by intratibial injection of PC-3MM2 cells (2 X 10^5 cells/20 µl) in male CD-1 nude mice using 27-gauge needle (2). Mice were imaged by DCE-MRI up to 5 weeks after intratibial injection.

Contrast materials: Biotin-BSA-GdDTPA was synthesized as previously reported (4). An intravenous dose of 10 mg/mouse was used.

MRI experiments: MR images were acquired on a 4.7T Biospec (Bruker Biospin, Billerica, MA) using micro-imaging gradients and a specially designed knee coil. T2-fSE: TR 4500 ms, TE 15.6 ms, 2 averages, matrix 256 X 192, FOV 30 X 30 mm, slice thickness 1 mm. 3D-fSPGR: flip angle 35 degrees, TR 10 ms, TE 1.23 ms, 2 averages, matrix 128 X 128 X 32, FOV 20 X 20 X 20 mm.

Histology: Limbs with tumors were excised, fixed in formalin, decalcified, embedded in paraffin and sectioned (4-6 µm). Tissue sections were stained for the biotinylated contrast material (4) and PDGF receptor (2).

Results

T2-weighted MRI showed that inoculation of PC-3MM2 cells into subcutaneous or muscle tissue resulted in rapid tumor growth. In contrast, a bone metastasis model, induced by intratibial injection of the same cells, resulted in relatively slow proliferation of cells in the bone marrow followed by osteolysis at the knee region and subsequent faster tumor progression. Normal tibia was hyperintense in T1-weighted contrast (biotin-BSA-GdDTPA) enhanced MRI due to the high vascularity of the bone. Tibia injected with tumor cells appeared normal in early stages (2-3 weeks; Fig 1 a) but signal intensity in the bone marrow was progressively lost as tumor cells proliferated towards the knee (Fig 1 b-e). Whereas tumor growth inside the bone was marked by signal loss (reduced enhancement), lysis of the bone and proliferation of the tumor cells in the surrounding tissue was characterized by accumulation of contrast material (increased enhancement) due to elevated vascular permeability (Fig 1 e; delayed enhancement indicated in green). At that stage, tumor growth in the muscle could be detected by T2-weighted MRI as well. Localization of tumor and biotinylated contrast material and expression of PDGF-Rβ were verified by histology.

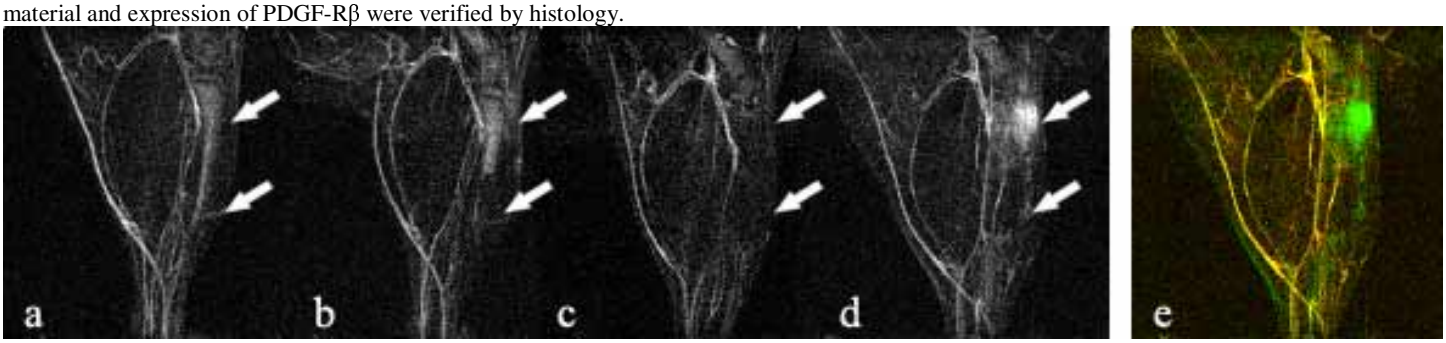

Figure 1. Maximal intensity projections (MIPs) of 3D-fSPGR images of the left hind limb obtained 2 (a), 3 (b), 4 (c) and 5 (d, e) weeks after the intratibial injection of PC-3MM2 cells (data from one representative mouse). The tibia is indicated by arrows. The MIPs represent 30 min postcontrast (a-d), after subtraction of the precontrast 3D dataset and overlay of the 1.5 (red) and 30 (green) min postcontrast (e).

Discussion

Hypo-intense bone metastasis was detected by DCE-MRI using macromolecular contrast material. The loss of contrast enhancement in the tibia probably resulted from contraction or collapse of blood vessels due to increased interstitial fluid pressure and the growing tumor mass in the confined bone compartment. In contrast, extravasation of contrast material was observed as the tumor proliferated beyond the bone, probably due to reduced pressure at the advancing tumor front. Interstitial hypertension is characteristic in many tumor types and some anti-tumor therapies can induce its reduction (5), including inhibition of PDGF-R (3). Results shown here suggest that contrast enhanced MRI can be used to monitor the normalization of bone vasculatre in response to therapy such as combination of PDGF-R inhibitor and chemotherapy (2).

References

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