Lymph Node Involvement of Hematologic Malignancies Detected Using the Magnetic Resonance Imaging with a Gadolinum Labeled Dendrimer Nanoparticle.

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Synopsis

There is a need for precise localization of patients' tumors with malignant lymphoma, as the presence of tumor outside of the lymph nodes alters both therapy and prognosis. A four-dimensional method of micro-MR lymphangiography (mMRL) using a nano-size, paramagnetic contrast agent (G6; 9 nm/ 240 kDa) coupled with a new sensitive pulse sequence [3D-fast imaging employing steady-state acquisition (3D-FIESTA-C)] to maximize the efficiency of this contrast agent is reported for visualizing lymphatic vessels, lymph nodes, and their relationship to hematologic tumors involving lymph nodes.

Introduction

Although 'traditional' chemotherapy and radiotherapy have made important contributions to improving the outcome of non-Hodgkin's lymphoma, this disease remains the fifth most common cause of death due to cancer while the incidence rate has been rising 4% per year for the past four decades. Extranodal involvement is one of the factors of malignant lymphoma associated with a poor prognosis. Since a new MR imaging sequence, 3D-fast imaging employing steady-state acquisition (3D-FIESTA-C) can image tissue based on T2/T1 signal, MRI acquired using 3D-FIESTA-C can depict both tumor tissue and paramagnetic contrast agents with better sensitivity than with T1-weighted sequences. Therefore, MRL taken with 3D-FIESTA-C has a potential to show the topological relationship between the lymphatic system and tumors in addition to tumor localization on a 3D display.

Methods

Contrast agent: A polyamidoamine-G6 dendrimer (58 kD) based nano-size MRI contrast agent coupled with 2-(*p*-isothiocyanatobenzyl)-6-methyl-diethylenetriamine-pentaacetic acid (1B4M) and 212 Gd(III) ions (240 kD; 9nm in diameter) to synthesize G6 to visualize the functional anatomy of the lymphatic system. ***Animal models:*** Ten week-old normal athymic mice were used for a comparative study between 3D-FIESTA-C and conventional 3D-fast spoiled gradient echo (3D-fSPGR) methods. Then two hematological tumor models; Karpas299, anaplastic large cell lymphoma and PT-18, mast cell tumor, were used for disease models. ***MRI studies:*** All mice were anesthetized and injected intracutaneously with 0.005 μmolGd of G6 into all middle phalanges for all mMRL studies. All dynamic micro-MR images were obtained using a 1.5-tesla superconductive magnet unit (Signa LX, General Electric Medical System) with a 1-inch round surface coil (Birdcage type) fixed by an in-house constructed coil holder. A 3D-FIESTA-C [TR/TE 10.8.4/2.2; 41.7 kHz, flip angle 45°, 2 NEX; scan time 3'42"] and a 3D-fSPGR [TR/TE 14.3/7.0; TI 43 msec; 31.2 kHz, flip angle 30°, 4 NEX; scan time 4'38"] with chemical shift fat-suppression were used for the contrast-enhanced dynamic lymphangiography studies. Serial images were obtained at 10, 20, 30, and 40 min post-injection of the contrast agents for 3D-fastSPGR and at 15, 25, 35, and 45 post-injection for 3D-FIESTA-C from each mouse. The coronal images were reconstructed with 0.6-mm section thickness with 0.3-mm overlap (two 512 matrix Zips). FOV was 8 x 4 cm and the size of matrix was 512 x 256 for 3D-fSPGR and 384 x 256 for 3D-FIESTA-C.

Results

Four lymph nodes, bilateral axillary and lateral thoracic, were visualized equivalently by both 3D-fSPGR and 3D-FIESTA-C by dynamic mMRL (Fig. 1). However, lymphatic vessels were visualized significantly better with 3D-FIESTA-C than with 3D-fSPGR at 10 and 40 min post-injection ($p<0.005$) due to the higher sensitivity of 3D-FIESTA-C to the G6 agent. This is due enhancement from the G6 contrast agent at a lower concentration at both earlier and later time points than the 3D-fSPGR (Fig. 1). In the Karpas299 lymphoma model mice, 3D-FIESTA-C superimposed the normal lymphatic system as white structures on gray tumors. This finding demonstrated that the tumors grew outside the lymphatic system (Fig. 2B). In contrast, in the PT-18 model mice, 3D-FIESTA-C showed lymphatic flows surrounding all axillary tumors. This finding demonstrated that the tumors grew in the axillary lymph nodes (Fig. 2A). Those findings were correlatively defined by histological analysis (Fig. 3).

Conclusion

Micro-MR lymphangiography using a new imaging method 3D-FIESTA-C and a nano-size paramagnetic contrast agent, G6, is a powerful combination, which enables to distinguish intra-lymphatic from extra-lymphatic sites of hematologic tumors in two animal models.

Fig. 1 3D-mMRLs of a normal mouse. A: 3D-fSPGR, B: 3D-FIEST-C,

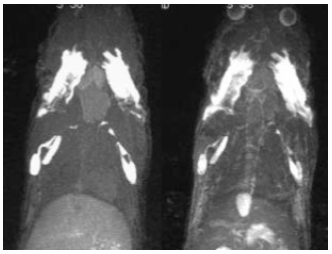

Fig. 2 3D-mMRL with 3D-FIESTA-C of tumor-bearing mice. A: PT-18 (in LNs), B: Karpas299 (outside of LNs),

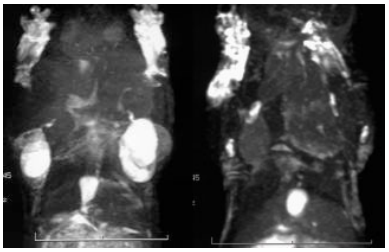

Fig. 3 mMRL vs histology correlation of a PT-18 tumor in a LN A: 3D-fSPGR, B: 3D-FIEST-C, C: H-E section.