Gadofluorine M and Magnevist Enhanced Imaging of the Mouse Lymph Nodes

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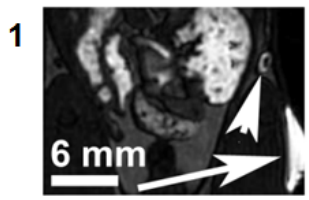
Target Audience: Scientists studying sentinel lymph node imaging, cancer metastasis imaging using contrast agent enhanced MRI

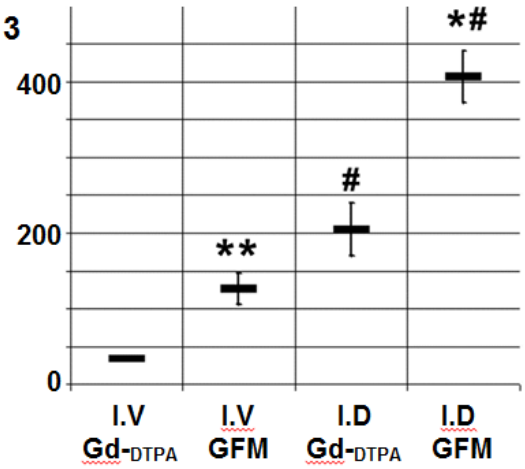
Purpose: The SLN is the first LN, or group of LN, to receive lymphatic drainage from a tumor. SLN dissection and histological analysis is often performed to determine if cancer has spread or not. Localization of the SLN is therefore very important. Contrast-enhanced MRI has been proposed as a tool (1) for improving the diagnostic accuracy of detecting the sentinel lymph nodes (LN) and stage. In this study we explored the use of a gadolinium-based contrast agent (CA) called Gadofluorine M (GFM) for the enhancement of murine LNs and we compared GFM to the more conventional Gd-DTPA (Magnevist) via two routes of administration. Furthermore, we were able to correlate the rather suspicious nature of enhancement in non-metastatic LN with normal LN architecture, and CA localization.

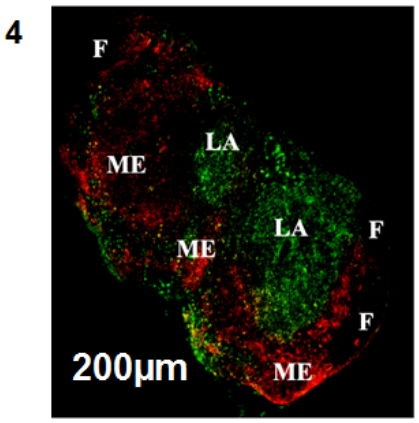
Methods: Healthy C57Bl/6 (N=5 per group; 4 groups) and C57BL/6 lys-EGFP-ki (N=4) mice, in which EGFP is expressed in all mature myelomonocytic cells including monocytes and macrophages as well as granulocytes (2), were injected with Gd-DTPA or GFM via intradermal (I.D) or intravenous (I.V) injections. Mice were imaged before and after CA administration using a ~25 minutes whole mouse body T1 weighted 3DSPGR (3D spoiled gradient recalled) imaging pulse sequence (TR/TE = 6.5/2.9, flip angle = 30º). Images were acquired at a resolution of 300 µm isotropic with 8 signal averages (8 NEX) at 1.5 Tesla. The signal intensity (SI) was measured by drawing regions of interest in the LNs for pre and post CA images. The signal enhancement ratio (SER) was calculated as follows: $SER = (SI_{post}/SD - SI_{pre}/SD)/(SI_{pre}/SD)$. The Student's t-test was used to compare the mean SER for different groups. Fluorescence microscopy images of 16µm sections were collected using a Zeiss Axio Imager (Germany) equipped with a Retiga EXi Digital CCD camera (Q Imaging, Vancouver, BC, Canada).

Results: After the administration of CA (e.g. Fig 1 Arrow at I.D injection into flank) all LN showed an increase in signal intensity (Fig 1. arrow head; enlarged view in Fig 2), for both routes and CA. However, GFM showed significantly greater ($p<0.5$) SER values (Fig 3. *# and **) compared to Gd-DTPA. I.D administration of GFM produced strong enhancement in primary and secondary draining LN, while I.V injection of GFM produced less enhancement but in at least 6 pairs of LN. The pattern of enhancement in LNs was ring-shaped (Fig 2), for all nodes and both CA, resulting in a central signal hypointensity. Fluorescence microscopy of nodes from mice injected with a red fluorescent version of GFM showed that the CA was preferentially localized in the medullary and cortical sinuses of the LN (ME) and not within the cellularly dense follicular (F) or lymphoid aggregates (LA) regions (Fig 4).

Discussions and conclusions: GFM is a promising CA for LN imaging. It has been shown that GFM binds to serum albumin, as well as collagens and proteoglycans (3), which could explain the preferential distribution and long retention of the CA seen within the LN sinuses rather than the cellularly dense areas. Caution should be taken so that the central region of signal loss observed post CA in normal mouse LN is not confused with pathology, which also often appears with low signal intensity.







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