Pitfalls of SPIO-enhanced MR Lymphography in Sentinel Lymph Nodes: Pathogenesis of High Signals Mimicking Metastasis in Inflamed Lymph Nodes

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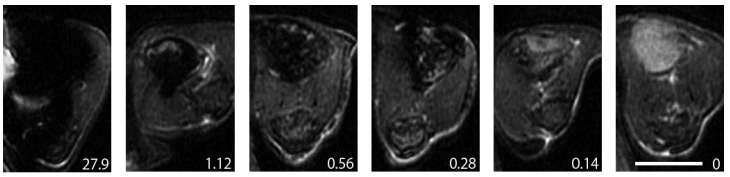
Introduction: Sentinel lymph nodes (SLNs) are lymph nodes (LNs) where lymph originating from primary tumors flows into first and, as a result, they are most often involved in lymphogenous metastasis. Superparamagnetic iron oxide (SPIO) and ultra-small SPIO (USPIO) -enhanced interstitial lymphography can differentiate metastatic SLNs from inflamed and normal SLNs, depending on the absence or presence of SPIO- or USPIO-laden macrophages [1-3]. It has been reported that the former appears as a total or partial high signal, whereas the latter two are homogeneous low signals. Recent studies, however, have demonstrated that non-homogeneous SPIO uptake in normal and inflamed LNs may produce focal high-signal areas mimicking metastatic foci [4, 5]. The purpose of this study was to investigate the relationship between SPIO doses and MRI findings in inflammatory LNs.

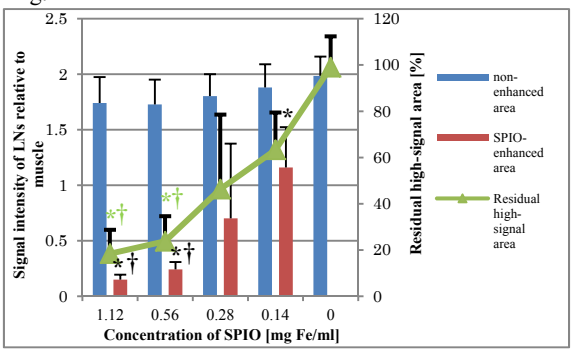
Materials and Methods: Our institutional animal experimental committee approved the animal experimental protocol. Male ddY mice (n = 34) were subcutaneously administered Freund's complete adjuvant in the dorsal foot pad to produce popliteal lymphadenitis [2, 5]. Two weeks later, T_2-weighted MR images (TR/effTE = 4000/60 ms, resolution = 78 x 78 x 1000 μm^3) of the popliteal LNs were acquired before and 2 hours after interstitial administration of 27.9–0.14 mg Fe/mL SPIO (ferucarbotran) using a 3-Tesla scanner and small solenoid coil. Seven mice received saline and served as a control. We assessed signal homogeneity in the popliteal LNs, calculated the residual high-signal (HS) area after SPIO administration by (HS area after SPIO / HS area before SPIO) x 100 [%], and determined the signal intensity of SPIO-enhanced and non-enhanced areas. These LNs were excised to evaluate the distribution of SPIO-derived iron with Prussian blue staining. We assessed F4/80-stained specimens in another cohort of mice (n = 5).

Fig.1



Results: Inhomogeneous negative enhancement was seen in 22/27 LNs (Table and Figure 1). In 5 cases, no enhancement was noted because SPIO could not reach popliteal LNs from the dorsal footpad, possibly as a result of an alteration in lymph flow. Strong susceptibility artifacts were frequently seen after 27.9 and 1.12 mgFe/mL SPIO administration. Residual high-signal areas and the signal intensity of SPIO-enhanced areas decreased as SPIO concentration increased (Figure 2). In specimens, SPIO-derived iron was noted in marginal and paracortical sinuses, where macrophages are present (Figure 3). F4/80-stained specimens showed a large number of macrophages at the periphery of LNs.

Fig.2



Discussion: Focal high-signal areas in inflamed LNs are possibly misinterpreted as metastatic foci. These high-signal areas were observed in a wide range of SPIO doses and not eliminated even if a sufficient amount of SPIO flowed into the paracortical sinuses at high doses. This was probably because some hyperplastic paracortices, where macrophages were not present, expanded more than 200 μm in width and produced high-signal pixels. At lower doses, a large number of macrophages at the periphery may cause inhomogeneous intra-LN distribution of SPIO. When applying SPIO-enhanced interstitial lymphography to cancer patients, attention must be paid to the intra-LN distribution of SPIO.

Conclusion: We found that the increase in interstitially-administered SPIO doses reduced, but did not eliminate high-signal areas mimicking metastases in inflamed SLNs. Radiologists should not interpret such high-signal areas as metastases.

References: [1] Weissleder R, et al. Radiology 1989;171:835-839 [2] Vassallo P, et al. Invest Radiol 1995;30:706-711 [3] Tanoura T, et al. Am J Roentgenol 1992;159: 875-881 [4] Johnson L, et al. Proc. ISMRM 2011;19: 1031 [5] Suzuki D, et al. Mag. Reson. in Med. Sci. (in press)

Table Signal intensity of the popliteal LNs after interstitial administration of SPIO with various doses

Concentration of SPIO [mgFe/mL]		27.9	1.12	0.56	0.28	0.14	0 (control)
Number of LNs		2	5	7	6	7	7
Signal in the popliteal LNs	Homogeneous high-signal	0	0	1	2	2	7
	Mixed-signal	0	5	6	4	5	0
	Homogeneous low-signal	2	0	0	0	0	0
Susceptibility artifact		2	4	0	0	0	0

Fig.3

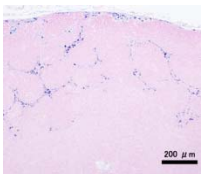


Fig. 1 T_2WI of popliteal LNs. SPIO concentrations are indicated at the lower right. Bar represents 5 mm.
Fig. 2 Bar chart showing signal intensities in SPIO-enhanced and non-enhanced areas as a function of SPIO concentration. Residual high-signal area is shown in the line graph. * P<0.01 compared to NS group. † P<0.01 compared to 0.14 mg Fe/kg SPIO group (Tukey's test)
Fig. 3 Prussian blue-stained specimen of inflamed LN. At the periphery, a large amount of SPIO-derived iron is noted as blue dots.