Lymphology 39 (2006) 156-163

MR IMAGING OF THE LYMPHATIC SYSTEM: DISTRIBUTION AND CONTRAST ENHANCEMENT OF GADODIAMIDE AFTER INTRADERMAL INJECTION

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ABSTRACT

We examined 24 lower extremities in 12 patients with lymphedema to evaluate the distribution and enhancement of gadodiamide after intradermal injection for MR imaging of lymphatic pathways in lymphedematous patients. The lymphedema was bilateral in 8, unilateral in 4, and 3 patients suffered from lymphedema in the genital region. 9 mL of gadodiamide and 1 mL of mepivacainhydrochloride 1% were divided into 5 portions and injected intradermally into the dorsal aspect of each foot. For MR imaging, a 3D spoiled gradient-echo sequence (Volumetric Interpolated Breathold Examination, VIBE) was performed. We detected the beaded appearance of lymphatic vessels extending from the injection site in 22 lower extremities (92%). In 13 lower extremities (54%), lymphatic vessels of the upper leg could be visualized. A contrast enhancement was observed in 16 out of 24 inguinal lymph node groups (67%). After 15 minutes of contrast material application, concomitant venous enhancement was detected in all lower extremities (100%). In 15 lower extremities (63%), collateral vessels with dermal backflow areas between lymphatic vessels were seen. Thus, intradermal injection of gadodiamide allows the visualization of lymphatic pathways in patients with lymphedema. In comparison to the venous system, lymphatic vessels show a tendency to have the highest contrast material uptake in the later acquisitions of 35, 45, and 55 minutes after intradermal injection of gadodiamide. Furthermore, 3D MIP reconstructions supported the identification of the lymphatic vessels and differentiation from veins due to the different angles of view.

Keywords: lymphatic imaging, magnetic resonance, gadodiamide, lymphedema, dynamic lymphangiomagnetogram, indirect interstitial lymphography

Lymphedema can be differentiated into primary (idiopathic) and secondary forms (1). In the secondary form, a known underlying pathology has caused low-output failure of the lymphatic system. In the primary form, the etiology is not yet entirely understood and may vary. In both forms of lymphedema, an accurate diagnosis and treatment plan must be based not only on the physical examination, but also on exact imaging modalities in order to assist the clinician in decision making (1-4). However, due to the complexity of visualizing the lymphatic vessels in human beings, no imaging procedure has fulfilled these criteria optimally (5-7). Interstitial magnetic resonance lymphangiography (i MRL) with intradermal injection of an extracellular, paramagnetic contrast agent is an innovative diagnostic imaging tool for the evaluation of pathologically changed lymphatic vessels (8,9).

The technique has proven to be safe and technically feasible in patients with primary and secondary lymphedema. The aim of this study was to evaluate the distribution and enhancement of gadodiamide after intradermal injection for MR imaging of lymphatic pathways in patients with lymphedema.

MATERIALS AND METHODS

Contrast Agent

Gadodiamide is a commercially available, extracellular, water-soluble, paramagnetic contrast agent with a gadolinium (Gd) concentration of 0.5 mmol. It is not metabolized and is excreted unchanged by passive glomerular filtration. Gd chelates have low molecular masses, and are quickly cleared from the intravascular space through the capillaries into the interstitial space. This contrast agent is normally administered intravenously at a recommended dose of 0.1 mmol per kilogram of body weight, which is equivalent to a dose of 0.2 ml/kg.

Study Design

Between September and December 2005, 24 lower extremities in 12 patients (mean age 47 years; range 25-71 years; 8 females, 4 male) with lymphedema of the lower extremities (11 primary, 1 secondary due to pelvic and inguinal lymph node extirpation suffering from malignancy) were examined with i MRL. The inclusion criteria was lymphedema of one or both lower extremities. Patients with contraindications for MRI, renal insufficiency, or a known gadolinium contrast agent allergy were excluded. This study had been approved by the local ethics committee, and all participants gave their informed consent before being included in the study.

Contrast Material Application

For injection of the contrast media, a thin needle (24 gauge) was used. A total of 9 mL contrast material and 1 mL mepivacain-hydrochloride 1% was divided into 5 portions and injected intradermally into the dorsal aspect of each foot at the region of the four interdigital webs and medial to the first proximal phalanx.

MR Imaging Examinations

MR imaging was performed with a 1.5-T system (Avanto; Siemens Medical Systems, Erlangen, Germany) equipped with high-performance gradients. Patients were placed in supine position with their arms beside the body. MR imaging was performed with spatial information from different elements of multiple independent radio-frequency receiver coils and channels.

Three locations were examined: first, the lower leg and foot region; second, the upper leg and the knee region; and third, the pelvic region and the proximal upper leg. A phased array body coil was used to image the pelvic region, and a dedicated peripheral surface coil was used to examine the upper and lower leg. Before i MRL, the lymphedema was imaged using a heavily T2-weighted 3D-TSE sequence (TR/TE: 2000/694; flip angle: 180°; matrix: 256 x 256, bandwidth: 247 Hz/pixel; 6/8 rectangular field of view 480 mm; slices: 96; voxel size: 2.0 x 1.9 x 1.7 mm; acquisition time: 4 min 48 sec). For i MRL, a 3D spoiled gradient-echo sequence (Volumetric Interpolated Breathold Examination, VIBE) was performed with the following parameters: (TR/TE: 3.58/1.47; flip angle: 35; matrix: 448 x 448, bandwidth: 490 Hz/pixel; 6/8 rectangular field of view with a maximum dimension of 500 mm; slices: 128; voxel size: 1.2 x 1.1 x 1.2 mm; acquisition time: 1 min 40 sec). The three locations were first imaged without contrast material and subsequently repeated 15, 25, 35, 45, and 55 minutes after intradermal application of the contrast material.

Image Analysis

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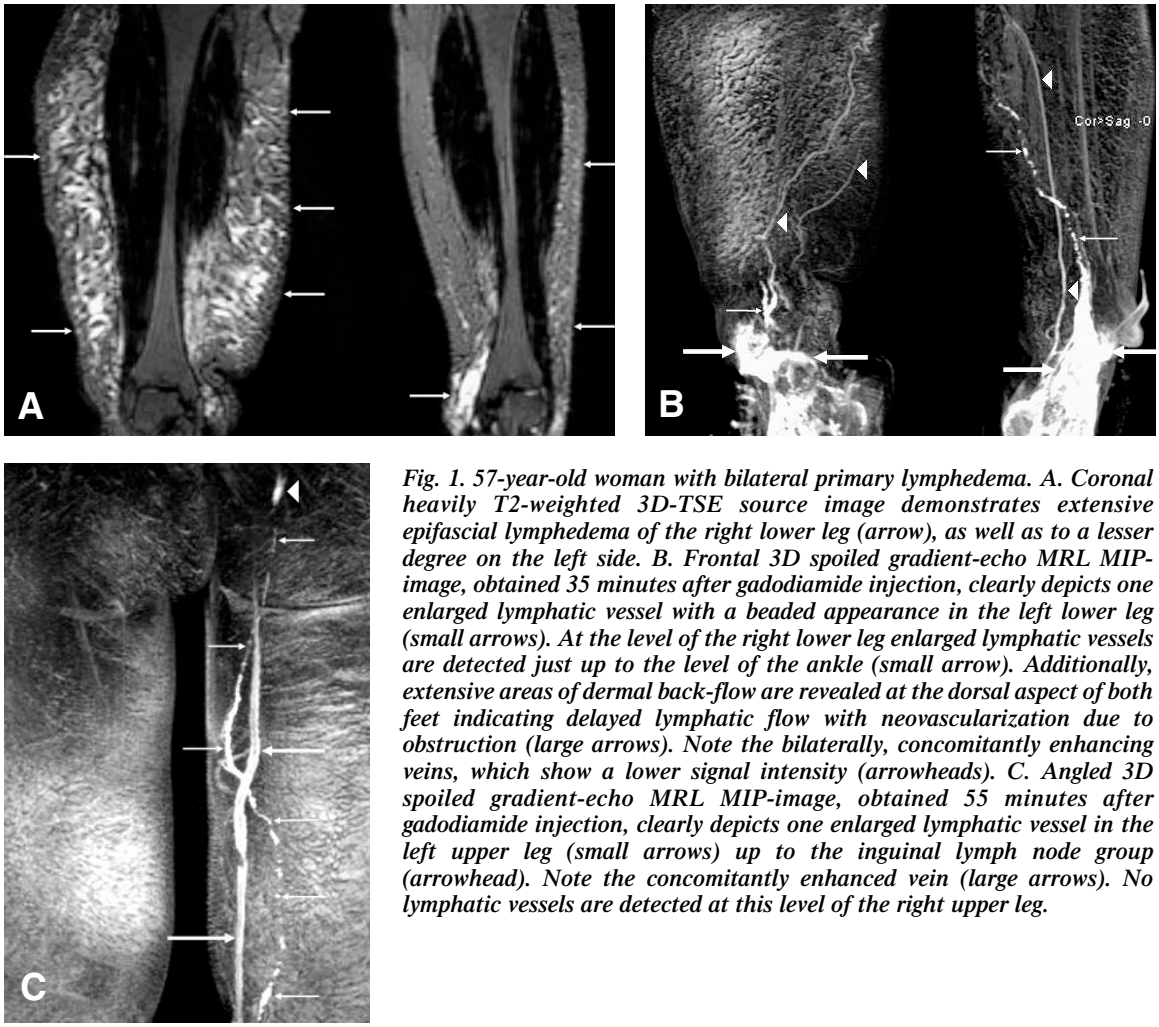

Fig. 1. 57-year-old woman with bilateral primary lymphedema. A. Coronal heavily T2-weighted 3D-TSE source image demonstrates extensive epifascial lymphedema of the right lower leg (arrow), as well as to a lesser degree on the left side. B. Frontal 3D spoiled gradient-echo MRL MIP-image, obtained 35 minutes after gadodiamide injection, clearly depicts one enlarged lymphatic vessel with a beaded appearance in the left lower leg (small arrows). At the level of the right lower leg enlarged lymphatic vessels are detected just up to the level of the ankle (small arrow). Additionally, extensive areas of dermal back-flow are revealed at the dorsal aspect of both feet indicating delayed lymphatic flow with neovascularization due to obstruction (large arrows). Note the bilaterally, concomitantly enhancing veins, which show a lower signal intensity (arrowheads). C. Angled 3D spoiled gradient-echo MRL MIP-image, obtained 55 minutes after gadodiamide injection, clearly depicts one enlarged lymphatic vessel in the left upper leg (small arrows) up to the inguinal lymph node group (arrowhead). Note the concomitantly enhanced vein (large arrows). No lymphatic vessels are detected at this level of the right upper leg.

qualitatively evaluated the enhancement of gadodiamide in the lymphatic pathways, inguinal lymph nodes and veins, using the source images and MIP reconstructions. The size of the regions of interest was adapted to encompass as much as possible of these structures. The postcontrast images facilitated the identification of these structures on the precontrast images. Noise was defined as the standard deviation of a measurement of signal intensity outside the patient. Signal-to-noise ratios were calculated by dividing the signal intensity by noise. Lymphatic vessels were evaluated regarding their visibility with a beaded appearance and size. An area of progressive dispersion of the contrast media into the soft tissues was regarded as dermal "back-flow" or differentiation. A diagnosis was made by consensus. The time course of enhancement of the lymphatic pathways, inguinal/iliac lymph nodes, and veins was analyzed by recording the maximal signal intensities.

RESULTS

The lymphedema was bilateral in 8 and unilateral in 4 patients. Three patients additionally suffered from a lymphedema in the genital region.

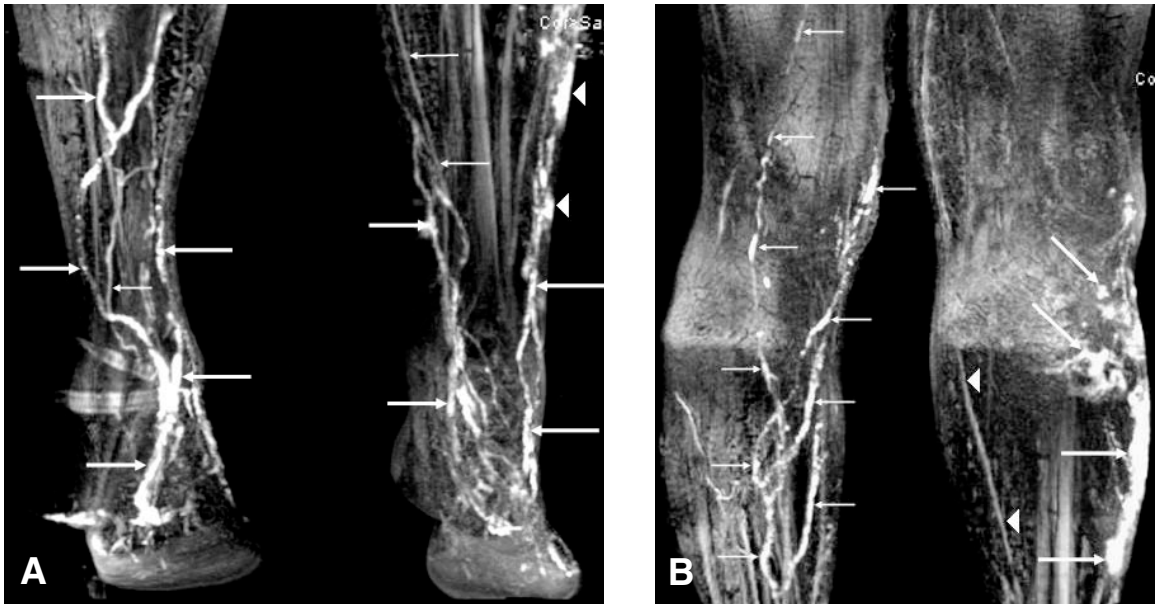

Fig. 2. 63-year-old man with bilateral primary lymphedema. A. Angled 3D spoiled gradient-echo MRL MIP-image, obtained 45 minutes after gadodiamide injection, clearly depicts several enlarged lymphatic vessels with a beaded appearance in both lower legs (large arrows). Furthermore, areas of dermal back-flow are revealed at the lateral aspect of the left lower leg, indicating delayed lymphatic flow with neovascularization due to obstruction (arrowheads). Note the bilaterally, concomitantly enhancing veins, which show a lower signal intensity (small arrows). B. Angled 3D spoiled gradient-echo MRL MIP-image, obtained 45 minutes after gadodiamide injection, clearly depicts several enlarged lymphatic vessels at the level of the right knee and right upper leg (small arrows). Extensive areas of dermal back-flow are revealed at the level of the left knee and proximal left lower leg, indicating delayed lymphatic flow with neovascularization due to obstruction (large arrows). Note the concomitantly enhanced vein in the left extremity, which shows a lower signal intensity (arrowheads).

The beaded appearance of lymphatic vessels extending from the injection site was detected in 22 lower legs (92%) *(Figs. 1B, 2A, 3; Table 1)*. The strongest contrast enhancement of the lymphatic vessels in the lower leg was present after 25 minutes in 2 lower extremities, after 45 minutes in 4 lower extremities, and after 35 and 55 minutes in 8 lower extremities *(Table 2)*.

In 13 lower extremities (54%), lymphatic vessels of the upper leg could be visualized *(Figs. 1C, 2B; Table 1)*. The highest signal intensities of the lymphatic vessels in the upper leg were present after 25 minutes in 2 lower extremities, after 45 minutes in 3 lower extremities, and after 35 and 55 minutes in 4 lower extremities *(Table 2)*.

A contrast enhancement was observed in 16/24 inguinal lymph node groups (67%) *(Fig. 1C; Table 1)* with the highest signal intensities measured in 8 lower extremities after 45 minutes, and in 8 lower extremities after 55 minutes *(Table 2)*.

After 15 minutes of contrast material application, concomitant venous enhancement was detected in the lower and upper leg of all lower extremities (100%) *(Figs. 1B, C, 2A, B, 3; Table 1)*. The strongest contrast enhancement of veins in the lower leg was present after 55 minutes in 2 lower extremities, after 15 minutes in 3 lower extremities, after 25 minutes in 4 lower extremities, after 45 minutes in 6 lower extremities, and after 35 minutes in 9 lower extremities *(Table 2)*. The highest signal intensities of veins in the upper leg were present after 55 minutes in 3 lower extremities, after 45 minutes in 4 lower extremities, after 25 minutes in 8 lower

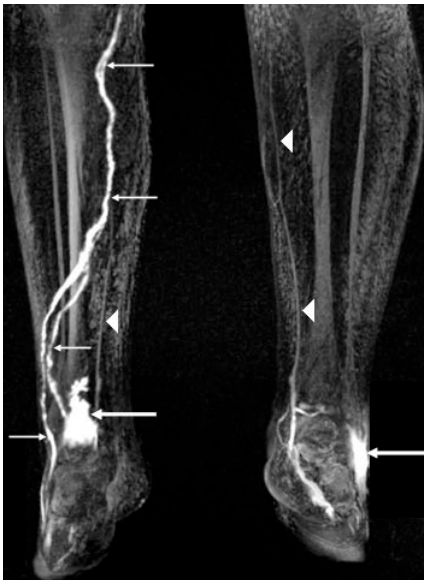

Fig. 3. 51-year-old woman with bilateral primary lymphedema. Frontal 3D spoiled gradient-echo MRL MIP-image, obtained 35 minutes after gadodiamide injection, clearly depicts two enlarged lymphatic vessels with a beaded appearance in the right lower leg (small arrows). No lymphatic vessels are detected at the level of the left lower leg. Furthermore, areas of dermal back-flow are revealed at the dorsal aspect of both feet, indicating delayed lymphatic flow with neovascularization due to obstruction (large arrows). Note the concomitantly enhanced veins in both lower extremities, which show a lower signal intensity (arrowheads).

extremities, and after 35 minutes in 9 lower extremities *(Table 2)*.

The external iliac lymph nodes were observed in only 5 patients, and paraaortic lymph nodes in one of the patients. In 15 of the 24 lower extremities (63%), collateral vessels with dermal back-flow between lymphatic vessels were seen, indicating proximal lymph flow obstruction with alternate pathways of transport *(Table 1)*. The maximum diameter of a dilated lymphatic vessel was 5 mm.

DISCUSSION

Due to the increasing number of patients suffering from lymphedema, the importance of clinical lymphology is increasing worldwide (1-4). Etiological classification differentiates between primary (idiopathic) and secondary lymphedema forms and in both types, lymphostasis leads to a development of high protein edema, accumulation of immune cells, fibrosclerosis, and deposition of fat (1).

Primary lymphedemas should be classified according to the onset of the disease. Lymphedemas which are present in the newborn are termed congenital lymphedema. Lymphedemas which occur in early childhood and before the age of 35 are termed as lymphedema praecox. Lymphedemas developing after the age of 35 are termed as lymphedema tardum, or late-onset lymphedema. Lymphedema praecox occurs mostly in females and may develop at any time prior to 35 years of age, but usually it appears between the ages of eleven and seventeen. The differentiation between primary and secondary forms of lymphedema is important. In older people, secondary lymphedemas due to malignancies are predominantly more common than the benign lymphedema tardum form (1). In both types of lymphedema, however, an accurate diagnosis and treatment plan must be based not only on the clinical findings, but also on exact imaging modalities, in order to assist the clinician in decision making (1-4).

To date, no imaging procedure has optimally fulfilled these criteria. At the present time, lymphoscintigraphy is considered the primary imaging modality in patients with lymphedema (5-7). This imaging procedure has, however, the disadvantage of ionizing radiation, and low spatial and temporal resolution. Conventional lymphography provides the highest concentration of the contrast media in lymphatic vessels and nodes (10). Due to long examination times, radiation exposure, invasiveness, and potential side effects, such as local wound infection and pulmonary embolism, the procedure is infrequently performed (11). Furthermore, in patients with clinically

TABLE 1
Interstitial Magnetic Resonance Lymphangiography Findings in 24 Lower Extremities with Lymphedematous Changes

HR MRL findings	Number of Lower Extremities (in percent)
Lymphatic vessel lower leg	22 (92%)
Lymphatic vessel upper leg	13 (54%)
Inguinal lymph node	16 (67%)
Concomitant venous enhancement lower leg	24 (100%)
Concomitant venous enhancement upper leg	24 (100%)
Collateral vessel	15 (63%)
Dermal back-flow area	15 (63%)

TABLE 2
Number of Lower/Upper Legs at the Time of Highest Contrast Enhancement after Intradermal Injection of Gadodiamide in Respect to Individual Lymphatic Vessels (LV), Veins (V) and Inguinal Lymph Node Areas (Ing. LN)

	LV, Lower leg	V, Lower Leg	LV, Upper Leg	V, Upper Leg	Ing. LN Area
15 minutes	0	3	0	0	0
25 minutes	2	4	2	8	0
35 minutes	8	9	4	9	0
45 minutes	4	6	3	4	8
55 minutes	8	2	4	3	8
Total	22	24	13	24	16

unilateral lymphedema, it has been suggested that the contralateral, clinically unaffected leg could become lymphedematous after conventional lymphography. Some authors are even of the opinion that direct oily lymphography is obsolete, since it is well known that in cases of unilateral lymphedema of the leg, the clinically normal leg may be in the latency stage, stage 0 of lymphedema (1).

Recently, i MRL with intradermal injection of a water-soluble, Gd containing contrast agent was shown to be safe and technically feasible in non-invasively displaying the lymphatic vessels and secondary complications in patients with primary and secondary lymphedema (8,9).

In accordance with previous i MRL studies, the beaded appearance of lymphatic

vessels extending from the injection site was detected in a large number of extremities in the present study (8,9,12,13). Presumably, due to dysplasia of the lymphatic system, no lymphatic collectors or inguinal lymph nodes were enhanced in two extremities. As a result of dysfunctional lymphatic drainage with dysplastic lymphatic vessels detected at the level of the lower leg, no lymphatic vessels in the upper leg and inguinal lymph nodes were seen in four extremities. The reason for non-visualization of two inguinal lymph node groups was prior extirpation due to malignancy.

In the four patients with unilateral lymphedema, enhancement of lymphatic vessels at the level of the lower leg and inguinal lymph node region was detected in all lower extremities without lymphedema. No external iliac lymph nodes or areas of dermal back-flow were observed in the extremities without lymphedema. The highest signal intensities of the lymphatic vessels in the lower leg were present 35 and 55 minutes, in the upper leg 45 minutes, and in the inguinal lymph node region 45 and 55 minutes after contrast material injection in the extremities without lymphedema.

In five extremities, three lymphedematous and two without lymphedema, it was not definitely possible to differentiate lymphatic vessels from veins on the basis of their beaded appearance at the level of the upper leg. We presumed that the lymphatic vessels were present since the inguinal lymph node groups enhanced regularly.

To further alleviate the differentiation of non-pathological enlarged lymphatic vessels from veins, an even higher spatial resolution and signal to noise ratio performing i MRL examinations is desirable. One option would be the use of MRI scanners with a higher field strength, e.g., the 3 Tesla system with total imaging matrix technology.

Due to venous uptake and renal clearance of the contrast media after intracutaneous injection, enhancement of the bladder was noted in all subjects as described in previous reports (8,9,12,13). The strongest concomitant venous enhancement, both in the lymphedematous and non-lymphedematous legs, was favorably detected in the images taken 25 and 35 minutes after injection.

As described previously, the enhanced lymphatic vessels in the lower/upper leg and inguinal lymph nodes demonstrated a tendency to having the highest contrast material uptake in the later acquisitions 35, 45 and 55 minutes after injection. This phenomenon is probably due to the slower flow velocity in lymphatic vessels compared to veins. It is important to mention, as in earlier i MRL studies using an extracellular, paramagnetic contrast agents, the lymph node enhancement was not sufficient for analysis of nodal morphology in the presented series (8,9).

In conclusion, intradermal injection of gadodiamide allows the visualization of lymphatic pathways in lymphedematous patients. In comparison to the venous system, lymphatic vessels show a tendency to have the highest contrast material in the later acquisitions 35, 45 and 55 minutes after intradermal injection of gadodiamide. Furthermore, 3D MIP reconstructions supported the identification of the lymphatic vessels and differentiation from veins due to the different angles of view.

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