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SHORT COMMUNICATION LYMPHATIC

Evaluation of Primary Lymphedema with Intranodal Lymphangiography

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Abstract

Purpose There are limited existing data on the lymphatic anatomy of patients with primary lymphedema (LED), which is caused by aberrant development of lymphatic channels. In addition, there is a paucity of contemporary studies that use groin intranodal lymphangiography (IL) to evaluate LED anatomy. The purpose of this retrospective observational study was to better delineate the disease process and anatomy of primary LED using groin IL.

Materials and Methods We identified common groin IL findings in a cohort of 17 primary LED patients performed between 1/1/2017 and 1/31/2022 at a single institution. These patients were clinically determined to have primary lymphedema and demonstrated associated findings on lower extremity MR and lymphoscintigraphy.

Results Ten patients (59%) demonstrated irregular lymph node morphology or a paucity of lymph nodes on the more symptomatic laterality. Eight patients (47%) demonstrated lymphovenous shunting from pre-existing anastomoses between the lymphatic and venous systems. Eight patients (47%) demonstrated passage of contrast past midline to the contralateral lymphatics. Finally, 12 patients (71%) failed to opacify the cisterna chyli and thoracic duct on their initial lymphangiograms. Delayed computed tomography of 3 patients showed eventual central lymphatic opacification up to the renal veins, but none of these patients showed central lymphatic opacification to the thorax.

Conclusion This descriptive, exploratory study demonstrates common central groin IL findings in primary LED to highlight patterns interventional radiologists should identify and report when addressing primary LED.

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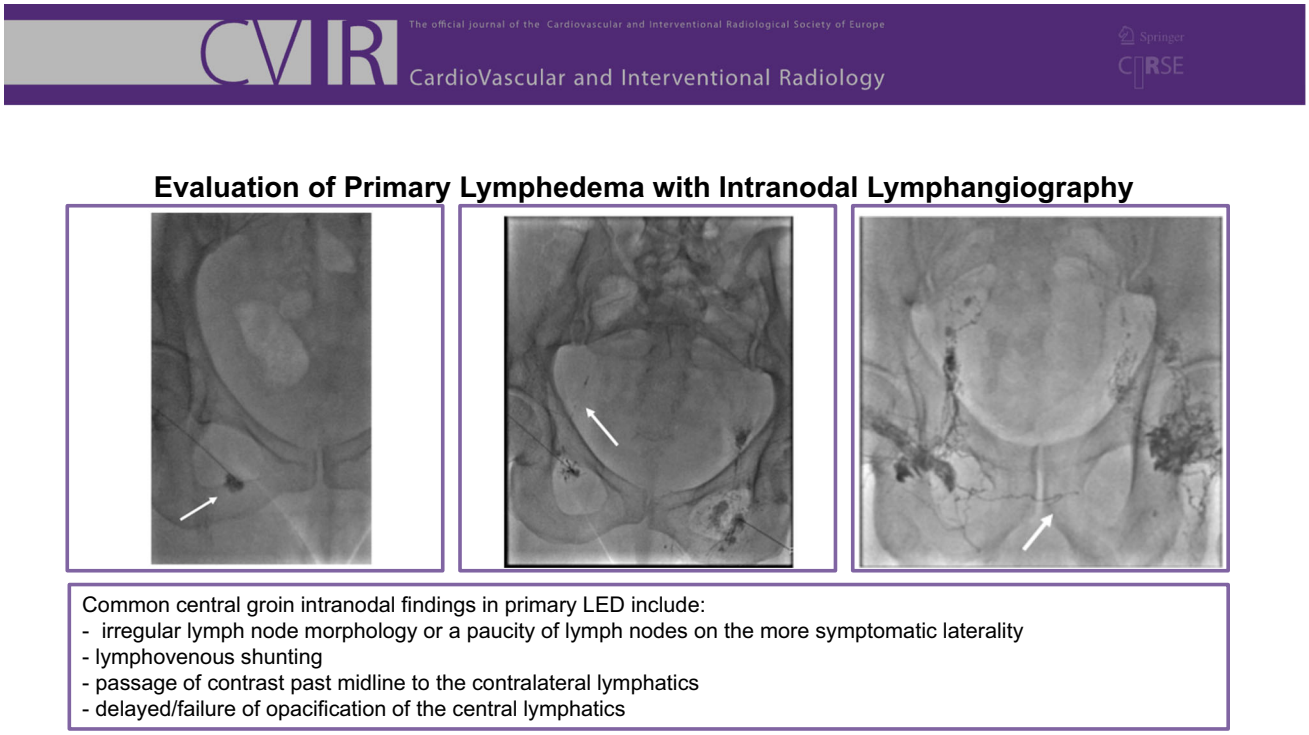
Graphical Abstract



Keywords Lymphedema · Primary lymphedema · Lymphangiography

Abbreviations

IL	Intranodal lymphangiography
LED	Lymphedema

Introduction

Lymphedema (LED) is the accumulation of lymphatic fluid in soft tissues due to impaired lymphatic drainage, resulting in inflammatory changes, fat hypertrophy, and fibrosis [1]. It negatively impacts quality of life, affecting ~ 10 million people in the USA [2] and 140,200 million people worldwide [3]. There are two subtypes of LED: primary, caused by aberrant development of lymphatic channels [1], and secondary, caused by an insult to previously normal lymphatic channels [1].

While the etiology of secondary LED is generally well-characterized, the disease physiology and anatomic aberrations involved in primary LED are less clear. Prior lymphangiography literature dating back to the 1960s (peripherally injecting the dorsal webspaces of the foot) [4, 5] and nuclear medicine studies dating back to the 1980s [6, 7] detail certain patterns more frequently seen with primary LED. For instance, 80% of primary LED patients demonstrate pre-existing lymphovenous anatomic anastomoses [7] versus 50% of secondary LED patients [8]. These values both exceed the 2–3% seen in the general healthy population [5]. Additional findings more prevalent in primary LED include: structural lymphatic abnormalities resulting collateral lymphatic filling, delayed clearance of contrast from lymphatic vessels [4], contralateral lymphatic abnormalities [4, 6], lymphatic aplasia [4], and delayed visualization of central lymphatics [4, 6, 7].

However, the prevalence of these findings in a primary LED cohort has not been investigated in the contemporary setting using intranodal lymphangiography (IL) from the groin. Notably, groin IL is different from standard peripheral lymphangiography because it directly accesses inguinal lymph nodes to observe central lymphatic flow, as opposed to focusing on peripheral lymphatics, thus decreasing procedure duration and reducing technical difficulties [9]. In addition, unlike dynamic contrast-enhanced MR lymphangiography, groin IL introduces the possibility for intervention and does not have the logistical challenges associated with performing needle placement within a strong magnetic field [10]. In this study, we describe our initial institutional experience delineating common groin IL findings in 17 primary LED patients.

Table 1 Details of patient demographics and laterality of symptoms

Patient	Sex	Age (years)	Prior procedures	Length of symptoms (years)	MR lower extremity	NM lymphoscintigraphy
1	F	72	None	51	Subcutaneous edema, fat hypertrophy	No tracer migration from injection sites
2	F	43	None	8	Subcutaneous edema, fat hypertrophy	Dermal backflow
3	F	70	None	51	Subcutaneous edema, fat hypertrophy	Dermal backflow
4	M	29	Right lower extremity debulking	11	Subcutaneous edema	Dermal backflow
5	F	37	None	30	Subcutaneous edema, fat hypertrophy	Dermal backflow
6	F	56	None	29	Subcutaneous edema, fat hypertrophy	Dermal backflow
7	F	54	None	5	Subcutaneous edema, fat hypertrophy	Dermal backflow
8	F	42	None	6	Subcutaneous edema, fat hypertrophy	Dermal backflow
9	F	75	Lymphovenous bypass on RLE	8	Subcutaneous edema, fat hypertrophy	Dermal backflow
10	F	52	None	41	Subcutaneous edema, fat hypertrophy	Focal nodal uptake
11	F	52	None	14	Subcutaneous edema, fat hypertrophy	Dermal backflow
12	F	33	None	6	Subcutaneous edema, fat hypertrophy	Not performed
13	M	60	None	41	Subcutaneous edema, fat hypertrophy	Dermal backflow
14	F	36	None	15	Subcutaneous edema, fat hypertrophy	Dermal backflow
15	M	37	Outflow stenting for May Thurner	1	Subcutaneous edema, fat hypertrophy	Dermal backflow
16	F	64	None	3	Not performed	Performed at outside hospital
17	F	44	None	24	Subcutaneous edema, fat hypertrophy	Dermal backflow

Materials and Methods

Patient Selection

The institutional review board at a single-institution tertiary referral center approved this HIPAA compliant retrospective study with waiver of informed consent. A manual search was conducted of the institutional radiology report database for angiography procedures categorized as "lymphangiograms" performed between 1/1/2017 and 1/31/2022. Seventeen primary LED patients (ages 29–75, 14 women) were identified for study inclusion. Prior to IL, all patients were evaluated at a Lymphedema Center of Excellence and were diagnosed with primary LED based on clinical history via lymphedema multidisciplinary conference. Additionally, per institutional protocol, all patients either underwent lower extremity MR and had abnormal results including subcutaneous edema and fat hypertrophy or underwent lymphoscintigraphy and had abnormal results including dermal backflow. Most patients (16/17) underwent both MR and lymphoscintigraphy with abnormal results (Table 1). IL was performed in these patients to further characterize lymphatic anatomic aberrations with the potential for endolymphatic intervention (e.g., central lymphatic stenting, plasty), although eventually none of the patients were found to have central lymphatic stenosis that was amenable to percutaneous intervention.

Primary Lymphedema Pattern Selection

Primary LED patterns were identified through a review of the literature with studies dating back to 1965. The patterns

Table 2 Common findings on IL across 17 patients with primary LED

Patient	Laterality of symptoms	Paucity of lymph nodes/atrophic lymph nodes	Lymphovenous shunting	Cross-over emptying	Visualization of central lymphatics to renal veins on initial lymphangiogram	Visualization of central lymphatics to thorax on initial lymphangiogram
1	Right	No	No	Yes	No	No
2	Left	No	Yes	Yes	Yes, on right	No
3	Left > right	Yes	No	No	No	No
4	Right	No	Yes	Yes	Yes	No
5	Left	Yes	No	Yes	Yes	No
6	Right	Yes	No	Yes	No	No
7	Right	Yes	No	No	No	No
8	Right	No	Yes	No	No	No
9	Right > left	Yes	Yes	Yes	No	No
10	Left	No	Yes	No	No	No
11	Right > left	Yes	Yes	No	No	No
12	Right > left	Yes	No	No	No	No
13	Right	No	No	Yes	Yes	No
14	Right = left	Yes	Yes	No	No	No
15	Left	Yes	No	No	No	No
16	Right = left	No	No	Yes	Yes	No
17	Right = left	Yes	Yes	No	No	No

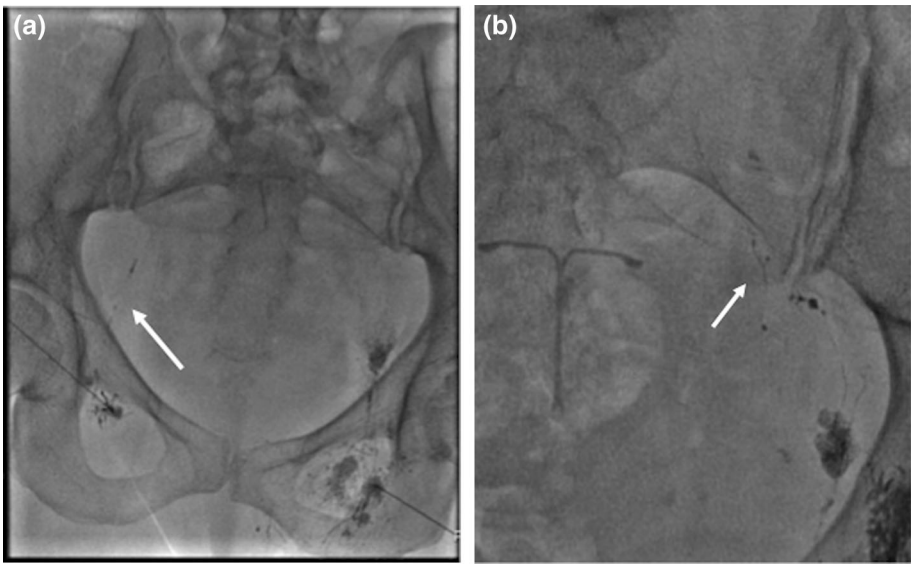


Fig. 1 **a** Lymphovenous shunting (arrow) demonstrated between the right-sided lymphatics and the right iliac vein in patient 17, a 44-year-old female with primary bilateral LED, right = left symptoms. **b** Lymphovenous shunting (arrow) demonstrated between the accessed left inguinal lymph node draining into the left iliac vein in patient 11, a 52-year-old female with primary bilateral LED, right > left symptoms

historically found to be more prevalent in primary LED were: irregular lymph node morphology/paucity of lymph nodes [4], lymphovenous shunting from pre-existing anastomoses between the lymphatic and venous systems [4], passage of contrast past midline to the contralateral lymphatics, and delayed/non-opacification of central lymphatics [4, 6, 7]. Reports from lymphangiograms from our primary LED cohort were reviewed for matching phrases of the above radiologic findings.

Intranodal Lymphangiography

All groin IL performed by an interventional radiologist with 11 years of experience. After nodal access was obtained, lymphangiography was performed as previously described by Nadolski and Itkin in 2012 [11], with modification of the technique for this indication. When bilateral groin nodal access was possible, 5 cc of lipiodol was slowly infused through 10-cc syringes into each groin node at a rate commensurate with visual progression of contrast

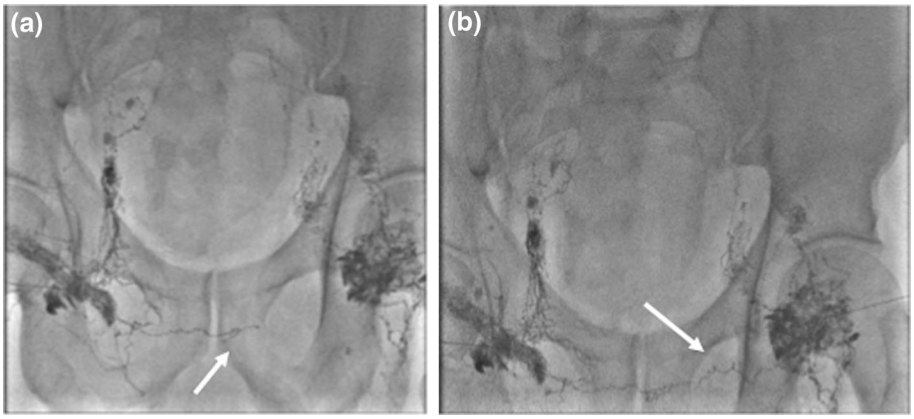


Fig. 2 **a** Initial cross-emptying (arrow) of lymphatic channels from the right inguinal lymph nodes into the left inguinal lymph nodes in patient 13, a 59-year-old male with primary right-sided LED. **b** Continued progressive cross-emptying (arrow) of lymphatic channels from the right inguinal lymph nodes into the left inguinal lymph nodes in the same patient

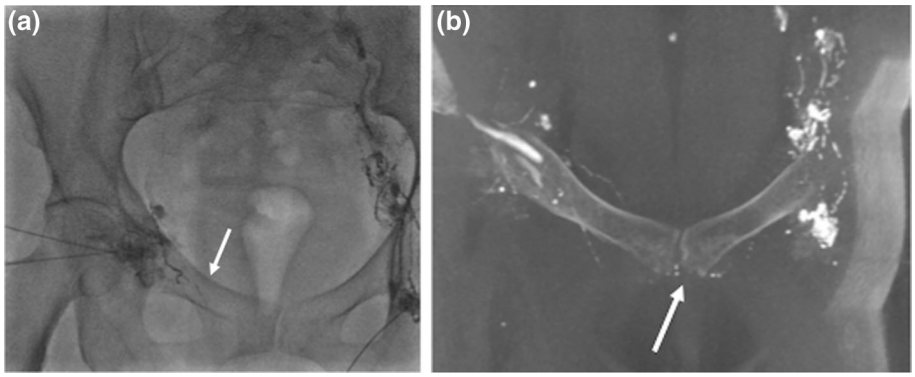


Fig. 3 **a** Initial cross-emptying (arrow) of lymphatic channels from the right inguinal lymph nodes into the left inguinal lymph nodes in patient 6, **a** 56-year-old female with primary right-sided LED. **b** Continued progressive cross-emptying (arrow) of lymphatic channels from the right inguinal lymph nodes into the left inguinal lymph nodes in the same patient, with communication seen at the level of the pubic symphysis

under fluoroscopy. After approximately every 1 cc of lipiodol, iodinated contrast (Optiray 320 contrast, Guerbet, Princeton, NJ, USA) was infused, pushing the lipiodol out of the node and into lymphatic channels. Care was used to minimize lipiodol usage with a limit of 10 cc given the embolic properties of lipiodol and to avoid the theoretical potential for transiently slowing lymphatic drainage on top of the existing lymphedema. Rotational cone-beam CT was performed at the operator's discretion to help delineate the lymphatic anatomy. Delayed CT was performed on patients where contrast did not progress beyond the pelvis during the procedure.

Results

All patients had lower extremity LED (Table 1), 7 bilateral, 6 right (Table 2). Common IL findings across primary LED patients were identified (Table 2). Ten patients (59%) demonstrated irregular lymph node morphology or a paucity of lymph nodes on the inguinal region of the more symptomatic laterality. Ultrasound images of the irregular lymph nodes were saved, and the presence of these findings was recorded in the procedure reports. Four of these patients (patients 7, 9, 12, 14) could only undergo unilateral lymph node cannulation due to irregular lymph node morphology or a paucity of lymph nodes on one side. Eight patients (47%) demonstrated lymphovenous shunting from pre-existing anastomoses between the lymphatic and venous systems (Fig. 1). Eight patients (47%) demonstrated passage of contrast past midline to the contralateral lymphatics (Figs. 2 and 3) from the affected side to the non-affected side, representing 6 with unilateral LED, 1 with right > left LED, and 1 with bilateral LED who had passage of contrast crossing midline from one affected side to the other (Table 2). Finally, 12 patients (71%) failed to opacify the cisterna chyli central lymphatics beyond the level of the renal veins on their initial lymphangiograms despite a median intraservice time of 105 min (75–285 min, Supplementary Table 3). A post-lymphangiogram CT abdomen/pelvis was performed on 9 of these patients who failed to opacify the cisterna chyli, after a median delay of 249 min (166–371 min), to evaluate whether the upper abdominal or thoracic central lymphatics

were eventually opacified. Of these 9 patients, only 3 eventually demonstrated central lymphatic opacification up to the renal veins, but none showed central lymphatic opacification up to the thoracic duct.

Discussion

This descriptive study demonstrates common central groin IL findings in primary LED to highlight patterns interventional radiologists should identify and report when addressing primary LED. This study collates findings from peripheral webspace-based lymphangiography and from nuclear medicine studies dating back to the 1960s. It represents a contemporary evolution of the LED literature by providing findings in a cohort of primary LED patients using the central groin IL technique.

Findings such as lymphovenous shunting are seen in 0–3% of normal healthy limbs according to prior anatomic [12], peripheral lymphangiogram [5], and nuclear medicine studies [13]. While the physiologic etiology of these findings in primary LED is not definitively known, delayed/non-opacification of the central lymphatics may be due to pre-existing developmental lymphatic aberrations [14] or inherent malfunction of lymphatic channels [15] in primary LED. Likewise, lymphovenous shunting may represent compensatory decompression of an abnormally high-pressure lymphatic system into the lower-pressure venous system [16]. Cross-emptying into the contralateral lymphatics may similarly represent compensatory decompression into less stenosed, lower-pressure lymphatic channels.

Notably, the role of both intranodal and peripheral MR lymphangiography in primary LED remains investigational, and there are no clear MR patterns identified in a primary LED cohort [17]. MR lymphangiography can generally demonstrate patterns of aberrant lymphatic drainage in LED as well as delayed drainage and venous shunting [18], but there are no MR studies that evaluate the prevalence of similar findings in a primary LED cohort. Future work should ideally expand this groin IL experience of primary LED patterns of drainage to different modern modalities including MR lymphangiography.

Extensively delayed transit of contrast, with no patients demonstrating transit into the chest, represents another potential area for future exploration. The delay may be due to an overall conduction delay or an underlying structural abnormality of the central lymphatics. Of note, we cannot exclude the possibility there was eventual passage of contrast beyond the time frame of the examination, either through the central channels or through collateral channels despite a median intraservice time of 105 min and delayed non-contrast CT hours after lymphatic contrast administration. Additional studies comparing our primary LED patient cohort with a separate cohort of patients who underwent lymphangiography for other etiologies can better define these abnormalities and their prevalence relative to a presumably unaffected cohort using contemporary groin IL. Patterns associated with laterality, severity, and LED onset may also be better correlated as experience increases with IL.

This study also has potential implications for primary LED therapy, which include location of lymph node transfer, benefits of lymphovenous bypass [19], and prognostication of future lymphedema in the contralateral side [8] in the context of our anatomic findings. For instance, lymph node transfer may be effective in patients with abnormal lymph node morphology or those who have a paucity of lymph nodes on the more symptomatic laterality. Similarly, lymphovenous bypass may be beneficial in creating more robust anastomotic channels in patients with pre-existing lymphovenous shunting.

The major limitation of this study is its small cohort size as well as its single-institution, retrospective nature. Furthermore, due to the small sample size, it was not statistically feasible to perform subgroup analyses based on the heterogeneity of primary lymphedema as a clinical entity [20]. Future work should evaluate these anatomic IL findings in an expanded cohort and involve continued observation, reporting, and more detailed description and documentation of these findings.

Conclusion

This descriptive, exploratory study demonstrates common central groin IL findings in primary LED to highlight patterns interventional radiologists should identify and report when addressing primary LED. These patterns include: irregular lymph node morphology or a paucity of lymph nodes on the more symptomatic laterality, lymphovenous shunting, passage of contrast past midline to the contralateral lymphatics, and delayed/failure of opacification of the central lymphatics.

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Declarations

Conflict of interest None of the authors declare relevant conflicts of interest in relation to this manuscript.

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