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Regional Patterns of Fluid and Fat Accumulation in Patients with Lower Extremity Lymphedema Using Magnetic Resonance Angiography

Joseph H. Dayan, MD^{1,2}, Itay Wiser, MD, PhD¹, Richa Verma, MD¹, Jody Shen, MD³, Nishi Talati, MD³, Debra Goldman, MS⁴, Babak J. Mehrara, MD^{1,2}, Mark L. Smith, MD⁵, Erez Dayan⁶, Michelle Coriddi¹, Alexander Kagan, MD³

¹Plastic and Reconstructive Surgery Service, Memorial Sloan Kettering Cancer Center, New York, New York

²Weill Cornell Medicine, New York, New York

³Department of Radiology, Mt. Sinai Health System, New York, New York

⁴Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

⁵Division of Plastic Surgery, Northwell Health System and Cancer Institute, Lake Success, New York

⁶Division of Plastic Surgery, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts

Abstract

Background: Fat accumulation is frequently observed in patients with lymphedema but is not accounted for in existing staging systems. Additionally, the specific regional patterns of fat and fluid accumulation remain unknown and might affect outcomes following medical or surgical

Corresponding Author: Joseph H. Dayan, M.D., 1275 York Avenue, Suite MRI 1005, New York, NY 10065, Tel: 212-639-8095, Fax: 212-717-3677, dayanj@mskcc.org.

Author Contributions:

Joseph H. Dayan – Study design, primary investigator.

Itay Wiser – Data analysis, manuscript writing.

Richa Verma – Data acquisition, manuscript editing.

Jody Shen – Data acquisition, methodology development.

Nishi Talati – Data acquisition, methodology development.

Debra Goldman – Statistical analysis.

Babak J. Mehrara – Study design, manuscript editing and revision.

Mark L. Smith – Study design, methodology development.

Erez Dayan – Data acquisition.

Michelle Coriddi – Data acquisition.

Alexander Kagan – Study design, methodology development, manuscript editing and revision.

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Products, devices, drugs, etc.: 1.5 Tesla MRI unit (GE Healthcare, Waukesha, WI), intravascular gadolinium agent, gadofosveset trisodium contrast agent, SAS 9.4 software (SAS Institute, Cary, NC).

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intervention. The purpose of this study was to evaluate fluid and fat distribution in patients with lower extremity lymphedema using magnetic resonance angiography (MRA).

Methods: MRA exams of patients with lower extremity lymphedema were reviewed. Fluid-fat grade and location were assessed by three observers. Three-point scales were developed to grade fluid (0 = no fluid, 1 = reticular pattern of fluid, 2 = continuous stripe of subcutaneous fluid) and fat (0 = normal, 1 = subcutaneous thickness less than twice that of the unaffected side, 2 = subcutaneous thickness greater than twice that of the unaffected side) accumulation.

Results: In total, 76 MRA exams were evaluated. Using the proposed grading system, there was good interobserver agreement for fat and fluid accumulation location (91.5%; $\kappa=0.9$), fluid accumulation grade (95.7%; $\kappa=0.95$), and fat accumulation grade (87.2%; $\kappa=0.86$). Patients with International Society of Lymphology (ISL) stage 2 lymphedema had a wide range of fluid and fat grades (normal to severe). The most common location of fluid accumulation was the lateral lower leg, whereas the most common location of fat accumulation was the medial and lateral lower leg.

Conclusions: The proposed MRA grading system may help stratify patients with ISL stage 2 lymphedema on the basis of tissue composition.

Introduction

Lymphedema is a debilitating disease commonly believed to result from progressive fluid accumulation. However, fat accumulation and fibrosis feature in the natural course of this disease.¹⁻⁵ Impaired lymphatic function and lymph stasis may lead to a chronic inflammatory state that stimulates collagen deposition and adipocyte accumulation over time.⁴

Although the phenomenon of fat accumulation is well-described, current staging systems for lymphedema are purely clinical and do not account for this variable. Patients undergoing surgical or nonsurgical interventions are typically assessed by limb volume difference and International Society of Lymphology (ISL) stage.⁶ However, the fluid and fat composition of the excess limb volume can vary considerably and may confound results, affect prognosis, and influence surgical decision-making. For example, we frequently observe that patients with the same ISL stage of lymphedema (in particular, stage 2) have markedly different patterns of fluid and fat excess. Additionally, the regional patterns of lymph accumulation and fibroadipose deposition have not been previously described. It is also unclear how the regions of fluid and fat excess relate to the location of the major lymphatic collectors of the lower limb.^{7, 8} Magnetic resonance angiography (MRA) is routinely used in our practice to provide information regarding not only fat and fluid composition but also vascular anatomy for lymph node transplant, and assess for potential vein stenosis and occult recurrence. The purpose of this study was to review these MRAs to evaluate the patterns of fluid and fat accumulation in patients with lower extremity lymphedema.

Methods

The institutional review board at Memorial Sloan Kettering approved this study (IRB 16-275). Patients who underwent MRA for primary or secondary lymphedema involving the lower extremity between December 1, 2012, and December 31, 2018, were retrospectively

identified from our prospectively maintained database. All MRA exams were performed by the same radiologist. Axial and sagittal high-resolution T1 fat-saturated gradient-echo images of the involved extremities were obtained after administration of a contrast agent. Intravenous gadolinium agent was used, and delayed-phase vascular imaging was obtained. MRA sequences were obtained on a 1.5 Tesla MRI unit (GE Healthcare, Waukesha, WI). Patients were scanned in the supine position, with a dedicated peripheral vascular coil. Coronal acquisition was obtained with T1-weighted postcontrast imaging without fat saturation using gadofosveset trisodium contrast agent. Axial and sagittal reformats were then obtained. Patients with lower extremity lymphedema were deidentified by an investigator not involved in the review process.

Assessment of Degree of Fat and Fluid Composition

The grading system proposed in this study was developed as a first attempt to stratify patients in a reasonable and reproducible way to evaluate their fluid and fat composition as we have observed a wide spectrum of differences in patients with the same ISL stage. It is admittedly subjective and an objective method is clearly preferable in the future. This is only an initial step toward this end and involved a lengthy process of identifying recurring patterns of fluid and fat accumulation. Working with an imaging software programmer, we initially attempted to quantify the absolute fluid and fat volumes on MRA. However, because of the presence of significant artifact, the use of absolute pixel brightness thresholds to differentiate between fluid and fat was not feasible. Consequently, we manually delineated the areas of interest for fat and fluid. Without an automated and reliable system, however, this was not practical for clinical use and was abandoned. We subsequently developed and tested different grading systems on the basis of viewing MRA sections representing the largest focus of lymphedema. These approaches were assessed for reproducibility, clinical relevance, and ease of use. Although more-involved grading systems were initially tested, lack of reproducibility and time-consuming methodology led to the current system presented in this paper. The recurring patterns of reticular formation of fluid accumulation within the fat, compared with the more-pronounced fluid excess, which resembled a contiguous stripe of lymph between fat and fascia, became easily recognizable. Although this grading system was qualitative, it provided a means to stratify patients with different tissue composition who otherwise have the same ISL stage. The following is a brief summary of the four ISL stages: (0) subclinical lymphedema: impaired lymphatic function without evidence of limb swelling, (1) mild lymphedema: mild but visible limb swelling that temporarily improves with elevation, (2) moderate lymphedema: moderate limb swelling with evidence of fibrosis that may or may not be associated with pitting edema which does not improve with elevation, and (3) elephantiasis: profound limb swelling with severe fibrosis, hyperkeratosis, and often verrucous skin changes.

Grading Process

For fluid and fat grading, coronal images were used to evaluate the largest area of swelling in the affected limb (lower leg, thigh, or both). The location of the highest concentration of fluid and fat was then recorded using coronal, axial, and sagittal sections. Finally, the dominant contributor to the limb volume excess was determined (fluid, fat, or codominant).

Next, the fluid and fat components were graded on a 3-point scale. Scoring for fluid accumulation grade was as follows: 0 = no fluid, 1 = honeycombing/reticular pattern of fluid within the subcutaneous fat, and 2 = continuous visible stripe of fluid between the fat and investing muscle fascia. Scoring for fat accumulation was as follows: 0 = no excess fat, 1 = fat accumulation less than twice the width of the widest fat stripe on the unaffected side, and 2 = fat accumulation greater than twice the width of the widest fat stripe on the unaffected side. Representative images of fluid and fat combinations observed on the basis of our MRA grading system are included as Figures 1–6.

Analysis of Interobserver Agreement

Images were deidentified and reviewed by three independent investigators, including a radiologist (A.K.), a plastic surgeon (J.H.D.), and a general surgery resident (R.V.). Overall percentage agreement and Light's kappa (κ) with bootstrapped 95% confidence intervals (CIs) were used to assess agreement among the three independent readers across 47 cases analyzed. Cohen's simple κ with 95% CI and percentage agreement were used to assess pairwise agreement among each pair of readers.

Statistical Analysis

Patients demographic characteristics, fluid and fat grade, predominance, and location were summarized on the basis of reads from a plastic surgeon (J.H.D.). The relationships between available patient characteristics and overall dominance, fat grade, and fluid grade were assessed using Fisher's exact test and the Kruskal Wallis test, where appropriate. ISL stages were then compared with results from our MRA grading system using Fisher's exact test. Analysis was performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Patient characteristics are listed in Table 1. A total of 76 patients were included in our study, of whom 82.9% (63/76) were female and 17.1% (13/76) were male. Malignancy accounted for the majority of cases, with gynecologic cancer being the most common cause of lower extremity lymphedema (32/76 [42.1%]; Figure 7). The mean duration of lymphedema was 125 months (range, 3–348 months; standard deviation, 113 months). Four patients had lymphedema for >30 years; 32.9% of patients (25/76) had lymphedema for <3 years. The average age was 51 years (range, 12–73 years), and mean BMI was 25.9 kg/m² (range, 17.0–42.0 kg/m²). Of the total 76 patients, 8 (10.5%) had ISL stage 1, 65 (85.5%) had stage 2, and 3 (4%) had stage 3 disease. Duration of lymphedema was not significantly associated with ISL stage ($r^2 = -0.13$; $p = 0.29$).

Fluid and Fat Distribution

The vast majority of patients in this series had some degree of fat accumulation (89.5%; 68/76). In our cohort, 10.5% of patients (8/76) had a fat grade of 0, 39.5% (30/76) had a fat grade of 1, and 50% (38/76) had a fat grade of 2. All but 2 patients (74/76; 97.4%) had clinical lymphedema with no evidence of fluid accumulation on MRA. Two patients (2/76 [2.6%]) had a fluid grade of 0, 48.7% (37/76) had a fluid grade of 1, and 48.7% (37/76) had

a fluid grade of 2. Fat was the dominant component of excess limb volume in 38.2% of patients (29/76), fluid was the dominant component in the same number of patients (29/76 [38.2%]), and fat and fluid contributed equally in 23.7% of patients (18/76). Fluid grade was positively but weakly associated with fat grade ($r^2 = 0.25$; $p = 0.029$). Overall fat or fluid dominance was not associated with age or sex. Lymphedema duration was not associated with higher grade of fluid ($r^2 = -0.03$; $p = 0.79$) or fat ($r^2 = -0.07$; $p = 0.52$) accumulation.

The most common locations of fluid and fat accumulation are presented in Table 2. The most common location of fluid accumulation was the lower leg (59/76 [77.6%])—in particular, the lateral lower leg (34/59 [57.6%]). Twelve patients (15.8%) had fluid accumulation in the thigh, most commonly the lateral thigh (5/12 [41.7%]). Only 5 patients (6.6%) had fluid accumulation distributed equally in the lower leg and thigh.

The most common site of fat accumulation was the lower leg (43/76 [56.6%]); the predominant distribution pattern in the lower leg was global (23/43 [53.5%]). When fat accumulation was present in the thigh, it was most commonly pronounced medially (13/18 [72.2%]). Fifteen patients (15/76 [19.7%]) had fat accumulation distributed equally in the lower leg and thigh.

Association Between ISL Stage and Fluid-Fat Grade

We next analyzed the data to determine whether ISL stage was associated with fluid and fat grade. Most of the patients in this study were diagnosed with ISL stage 2 lymphedema (65/76 [85.5%]). Fluid grade was not significantly associated with ISL stage (Figure 8). In contrast, fat grade was significantly associated with ISL stage (Figure 9). For example, only 12.5% of patients with ISL stage 1 disease had a fat grade of 2, whereas approximately half of patients with ISL stage 2 disease had a fat grade of 2, and 100% of patients with ISL stage 3 disease had a fat grade of 2. These findings demonstrate a highly variable mix of fluid and fat grades across ISL stages. This is most striking in patients with ISL stage 2 lymphedema, among whom nearly every combination of fluid and fat grade was represented.

Interobserver Agreement

Agreement between the three readers was high (Table 3). Agreement for overall fat or fluid dominance was 91.5% (Light's $\kappa = 0.90$; 95% CI, 0.78-0.98). Concordance for location of both fat and fluid accumulation was 91.5%. Interobserver agreement was 95.7% ($\kappa = 0.95$; 95% CI, 0.83-1.00) for fluid grade and 87.2% ($\kappa = 0.86$; 95% CI, 0.70-0.95) for fat grade. Overall, the interreader agreement for this grading system was high, making this a reasonable starting point for grading the fluid-fat excess in patients with lymphedema.

Discussion

The findings in this study demonstrate that fat accumulation is a prominent feature of lymphedema and may be an important factor in patient assessment. Nearly 90% of patients had some degree of fat accumulation, and fat was the dominant component of excess limb volume in more than one-third of patients. This demonstrates the significance of the contribution of fat to limb volume and may account for variable outcomes following lymphatic reconstruction or decongestive therapy. Many current outcomes studies focus on

limb volume and bioimpedance, which have inherent limitations.⁹ Limb volume does not account for the fluid-fat composition. Bioimpedance is an indirect means of measuring extracellular fluid content, which may be low in a fat-dominant limb even though the patient may have advanced disease.¹⁰ Although the grading system proposed in this study is limited by its qualitative nature, it does provide a simple and useful method to stratify patients on the basis of fluid-fat composition. This is a significant confounding variable when studying any medical-, surgical-, or physiotherapy-based intervention and is not specifically accounted for in existing staging systems. An ideal method of grading fluid and fat would be quantitative. We are currently evaluating several techniques for obtaining quantitative data that would be feasible in a clinical setting.

The specific patterns of fat and fluid accumulation are also of interest and do not appear to have any relationship to the location of the dominant ventromedial lymphatic collectors of the lower extremity.⁸ This may be relevant to cases of lymphatic reconstruction. Typically, lymph node transplants are placed along the ventromedial axis.^{11–13} Placing lymph nodes laterally, where most of the fluid accumulates, may be worth investigating in the future.

Curiously, the duration of lymphedema was not associated with either fluid or fat grade or ISL stage. The ability to draw conclusions from this may be limited by the distribution of ISL stages among the patients in this study. However, patients with a short duration of lymphedema and early ISL stage had profound fat accumulation. For example, 25% of patients with a severe fat grade of 2 had lymphedema for <2 years. This counters the generalized notion that fluid is serially replaced by fat in a linear relationship over time. The lack of a time-dependent association with fat or fluid accumulation suggests that these patients do not all fall along the same spectrum of disease. These variable manifestations of fibrofatty accumulation likely reflect fundamental differences in immune pathophysiology among patients, with some forms of lymphedema that are more aggressive and proliferative than others. Additionally, some patients have intractable cellulitis (the cause of which stills remains unclear), whereas others do not.¹⁴ These findings may have implications for how we conduct studies among patients with lymphedema. Instead of approaching patients with lymphedema as a homogeneous population, patients may be specifically stratified into groups—for example, fat dominant, fluid dominant, cellulitis-prone, and no history of infection. The differences observed among patients may explain the variable outcomes following any intervention and may allow us to better direct specific treatments to the most appropriate subgroups of patients.

Understanding a patient's fluid-fat composition may help determine the most appropriate clinical approach for them. A limb with advanced fibrofatty proliferation may not respond well to decongestive therapy or physiologic procedures, such as vascularized lymph node transplant and lymphaticovenous anastomosis. In these cases, liposuction, as advocated by Brorson et al., has been beneficial, as long as there is no significant pitting and the patient is 100% compliant with compression.^{15, 16} In contrast, a fluid-dominant limb may respond better to decongestive therapy, vascularized lymph node transplant, or lymphaticovenous anastomosis. However, as observed in this study, many patients have a combination of fluid and fat excess, and multimodal treatment may be most appropriate for such patients. Ideal timing and patient selection remain topics of debate.^{17, 18}

The staging of lymphedema is currently dominated by systems that use physical exam alone and is inadequate in the modern era of imaging and biomarkers. The basic approach to staging affects the level at which we approach the disease and, in turn, the treatment offered to patients with lymphedema. In this study, the majority of patients had ISL stage 2 disease. However, within this group, there was a wide array of fluid and fat compositions. In effect, the use of MRA has unmasked significant differences in patients with the same ISL stage of lymphedema. For example, Figures 4 and 5 demonstrate two patients with ISL stage 2 lymphedema who have similar limb volumes but completely inverse fluid-fat ratios. Consequently, it is likely that these two patients may have different outcomes following a new medical treatment, surgical intervention, or physiotherapy. In our practices, we routinely review the results of our MRA grading system with patients so that they can better understand why they are likely or unlikely to respond to treatment.

As imaging techniques continue to improve and further insights into the pathophysiology of lymphedema are made, staging of lymphedema will continue to evolve. The system proposed here provides only a fluid-fat grade and is not a staging system. It is meant to complement and contribute to a more complete staging of a patient's lymphedema. The consideration of additional components, such as physiologic function¹⁹ and, one day, pathophysiologic grade, will help to provide a more complete view of the patient's overall disease burden. There is currently no single imaging modality or staging system that adequately reflects the status of a patient's lymphatic system in total. MRA serves to fill a gap, providing information not only on fluid-fat composition but also on the status of the venous system, the vascular anatomy (which can inform surgical planning), and the presence or absence of occult cancer. Thus, MRA has become a key component of our clinical workup as well as an important part of studies investigating outcomes after lymphatic surgery.^{20–22} This fluid-fat grading system is not intended to be used in place of existing staging systems but as an additional tool to clarify differences among patients. In summary, the closer we delve into lymphatic imaging, the more clear it becomes that staging of a lymphedema patient using physical examination alone is inadequate.

Conclusions

Knowledge of the local patterns of fluid and fat accumulation and of the overall tissue composition is important to understand the individual nature of a patient's lymphedema. Current lymphedema staging systems are inadequate, as they do not specifically differentiate patients on the basis of these confounding variables. The fluid-fat grading system proposed in this study is a simple and reliable way of stratifying patients and can serve as a complement to existing clinically based staging systems. This grading system may be useful for evaluating patients and planning treatment and may help to identify the influence of fat and fluid factors on outcomes.

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Figure 1.
Normal-appearing coronal section of lower extremity MRA demonstrating fluid 0/fat 0 grades: no fluid or fat accumulation .

Figure 2.

Coronal section of lower extremity MRA demonstrating fluid 1/fat 0 grades: mild fluid accumulation laterally without any fat accumulation. Orange arrow indicates a reticular pattern of fluid in the left lateral lower leg, consistent with fluid grade 1.

Figure 3.

Coronal section of lower extremity MRA demonstrating fluid 2/fat 0 grades. Orange arrows indicate profound lymph accumulation throughout the right lower leg, without significant fat accumulation. The contiguous fluid stripe along the lateral leg is consistent with fluid grade 2.

Figure 4.

A, Clinical photo of a patient with lower extremity lymphedema consistent with ISL stage 2, who has a similar limb volume difference as the patient in Figure 5A but significantly different fluid and fat composition, as seen in Figures 4B and 5B. B, Coronal section of lower extremity MRA of the patient presented in Figure 4A demonstrating fluid 2/fat 1 grades: pronounced lymph accumulation with a continuous fluid stripe in the lateral lower leg (fluid grade 2) with mild fat accumulation mostly in the medial calf (fat grade 1).

Figure 5.

A, Clinical photo of a patient with lower extremity lymphedema consistent with ISL stage 2, who has a similar limb volume difference as the patient in Figure 4A but significantly different fluid and fat composition. This patient's limb has very little fluid accumulation and mostly fat accumulation. These two patients may respond differently to surgery or decongestive therapy despite similarity in limb volume differences. B, Coronal section of lower extremity MRA of the patient presented in Figure 5A demonstrating fluid 1/fat 2 grades: mild fluid accumulation laterally with honeycombing pattern (fluid 1) and pronounced fat accumulation throughout the lower leg (fat 2).

Figure 6.

Coronal section of lower extremity MRA demonstrating fluid 2/fat 2 grades: profound fluid and fat accumulation throughout the right thigh. The majority of fluid is in the lateral compartment, whereas a significant amount of the fat accumulation is in the medial compartment.

Figure 7.
Etiology of lymphedema in this series.

Figure 8.
Percentage of fat grades by each ISL stage and their correlation.

Figure 9.
Percentage of fluid grades by each ISL stage and their correlation.

Table 1.

Patient characteristics (N=76)

Characteristic	Mean (Range) or No. (%)
Age, years	51 (12-73)
Sex	
Female	63 (83)
Male	13 (17)
Body mass index, kg/m ²	26 (17-42)
History of radiation treatment	
Yes	31 (41)
No	45 (59)
Duration of lymphedema, months	125 (3-348)
ISL stage	
1	8 (11)
2	65 (86)
3	3 (4)

Table 2.

Distribution of fluid and fat accumulation in the lower extremity by dominant location and laterality

Distribution Pattern	<i>Location</i>			<i>Total</i>
	Lateral	Medial	Global	
Fat				
Thigh	2 (11)	13 (72)	3 (17)	18
Lower leg	3 (7)	17 (40)	23 (53)	43
Both	0 (0)	5 (33)	10 (67)	15
Fluid				
Thigh	5 (42)	3 (25)	4 (33)	12
Lower leg	34 (58)	7 (12)	18 (30)	59
<i>Both</i>	<i>3 (60)</i>	<i>0 (0)</i>	<i>2 (40)</i>	<i>5</i>

Data are no. (%).

Table 3.

Overall interobserver agreement between three independent readers

Variable	Agreement, %	Light's kappa (95% CI)
Overall dominance	91.5	0.90 (0.78-0.98)
Fat location	91.5	0.89 (0.75-0.97)
Fat grade	87.2	0.86 (0.70-0.95)
Fluid location	91.5	0.78 (0.46-0.95)
Fluid grade	95.7	0.95 (0.83-1.00)