Cureus
Part of SPRINGER NATURE

Open Access Original Article

Asymmetric Lipedema With a Coexisting Local Condition: A Retrospective Case Series and a Local-Amplification Hypothesis

Review began 10/23/2026
Review ended 11/18/2026
Published 11/27/2026

© **Copyright** 2026
Amato et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.120359

Alexandre C. Amato [1], Juliana L. Amato [2], Keller S. Santos [3], Daniel A. Benitti [1]

1. Vascular Surgery, Amato Duo, São Paulo, BRA 2. Gynecology and Obstetrics, Amato Duo, São Paulo, BRA 3. Vascular Ultrasound, Amato Duo, São Paulo, BRA

Corresponding author: Alexandre C. Amato, alexandre@amato.com.br

Abstract

Introduction: Lipedema typically presents as a symmetrical, bilateral enlargement of the limbs, although international consensus acknowledges that asymmetry may occur in the presence of comorbidities. Asymmetric presentations are rarely described, and whether a local condition modifies the disease in one limb is unknown.

Materials and methods: Retrospective case series of women with clinically diagnosed lipedema and asymmetric lower limbs, purposively selected as illustrative cases from more than 1,100 patients assessed with segmental bioimpedance (vascular referral center, São Paulo, Brazil, 2020 to 2026), using contemporaneous records, standardized chart photographs, and photogrammetric perimetry, with venous duplex, lymphatic assessment, cross-sectional imaging, and subcutaneous ultrasound where performed.

Results: Six women were included (25-64 years; body mass index 25.2 to 35.9 kg/m^2). The more affected limb carried varicose vein disease (with an unconfirmed suspicion of Klippel-Trénaunay syndrome), saphenous reflux and a previous knee injury, May-Thurner syndrome in a patient with a previous tibial fracture, post-infectious lymphedema, a pelvic-inguinal lymphatic abnormality, or knee chondromalacia (with genu valgum on photographs). A limb injury preceded the asymmetric worsening in three patients, and imaging reported subcutaneous edema in the affected limb in three. The affected limb, or its lower leg, was visibly larger on photographs in all six, with a greater estimated circumference at the mid-lower-leg level in all six, whereas the contralateral thigh was larger at two or more levels in two. The affected leg had the lower bioimpedance fat percentage in all six, by 3.8 to 7.1 percentage points in four (arms, ⩽1.0 point).

Conclusions: In all six patients, selected for asymmetry and a documented condition, the visibly larger, more affected limb carried a coexisting venous, lymphatic, post-traumatic, or articular condition, and imaging reported edema in three. Asymmetry should prompt a lymphovenous work-up rather than exclusion of lipedema. These cases motivate, but do not test, the hypothesis that local stasis and inflammation amplify lipedema.

Categories: Cardiac/Thoracic/Vascular Surgery, Endocrinology/Diabetes/Metabolism
Keywords: asymmetry, bioelectrical impedance, case series, chronic venous disease, lipedema, lymphedema

Introduction

Lipedema is a chronic disorder of subcutaneous adipose tissue characterized by disproportionate enlargement of the limbs that typically spares the hands and feet, accompanied by pain and easy bruising [1]. Prevalence estimates in adult women range from less than 1% to 12% [2], and an estimated 12.3% of Brazilian women are affected [3]. The diagnosis is currently made on clinical grounds [4], and lipedema is often misdiagnosed [5].

Symmetry has been part of the definition since the original description, in which the enlargement of the limbs "has always been generalized and symmetrical" [6]. The German S2k guideline states that the disproportion occurs "always symmetrically" [7], the United States standard of care lists symmetric tissue among its diagnostic considerations [8], a research case definition requires symmetrical deposition [9], and symmetrical involvement was present in more than 80% of a prospective cohort [10]. The 2023 Lipedema World Alliance Delphi consensus, however, states that untreated lipedema "typically presents as symmetrical, bilateral" enlargement and adds that "some patients may demonstrate asymmetry as the disease progresses or in the presence of comorbidities" [2]. In a national survey of 707 women with a lipedema phenotype, 13-24% reported an asymmetric appearance of the hips, knees, thighs, or calves [11]. Detailed clinical descriptions of such presentations are nonetheless scarce; one report describes a lipedema that began unilaterally in a limb with a previous deep venous thrombosis and later became bilateral [12].

Marked asymmetry rightly raises the possibility of lymphedema or chronic venous disease. These conditions

are not mutually exclusive with lipedema and may coexist in the same patient [13]: venous disease is common in women with lipedema [8,14], lymphoscintigraphic abnormalities were found in 47% of patients with lipedema in a prospective cohort [15], and, in the evaluation of leg edema, bilateral but asymmetric cases may reflect "a unilateral cause superimposed on a background of systemic disease" [16]. Clinical criteria that separate lipedema from lymphedema were, moreover, derived largely from symmetrical presentations [17].

Lipedema adipose tissue shows an M2-polarized (alternatively activated) macrophage infiltrate that influences adipocyte differentiation [18], stage-dependent adipocyte hypertrophy and fibrosis [19], increased endothelial permeability [20], capillary wall alterations [21], dysregulated proliferative signaling in adipose-derived stem cells [22], and raised vascular endothelial growth factor C (VEGF-C) with macrophage infiltration [23]. Outside lipedema, experimental lymphatic fluid stasis produces an inflammatory response followed by subcutaneous fat deposition [24,25]. Together, these observations raise the possibility that a local source of stasis or inflammation could amplify lipedema in one limb.

We describe six women with lipedema and clinically asymmetric lower limbs. Our aims were to document, from contemporaneous records, the coexisting condition and the lymphovenous work-up in each patient; to characterize the nature of the asymmetric excess with the tools available; and to set out, with its limitations, the hypothesis that local stasis and inflammation amplify lipedema. The study is descriptive and hypothesis-generating, and two of the tools available, photogrammetric perimetry and segmental bioimpedance, are not validated for measuring adipose tissue in an edematous limb; they were used only to compare the two limbs of each patient. We use “asymmetric lipedema” descriptively, for a clinically evident difference between the lower limbs of a woman with lipedema; the term does not imply that the lipedema adipose tissue itself is asymmetric, because the excess may include edema or tissue belonging to the coexisting condition.

Materials And Methods

Design, setting, and ethics

This was a retrospective, descriptive case series from a vascular referral center in São Paulo, Brazil. Reporting follows the CARE (CAse REport) guidelines where applicable [26], and the methodological domains proposed for case series (selection, ascertainment, causality, and reporting) are addressed explicitly [27]. The study was approved by the Research Ethics Committee of the University Hospital of the University of São Paulo (CEP-HU/USP; ethics review number, CAAE, 00880826.1.0000.0076) and complied with the Declaration of Helsinki.

Case identification

Women with a chart diagnosis of lipedema and clinically asymmetric lower limbs whose records fell between February 2020 and January 2026 were reviewed by the treating vascular surgeon. Inclusion required a clinical diagnosis of lipedema, clinically asymmetric lower limbs, and an identifiable condition in one limb. From the records of more than 1,100 patients who underwent segmental bioimpedance at the center during the study period, six were purposively selected as illustrative cases, on the basis of a clearly visible interlimb difference on the standardized photographs and a documented coexisting condition; this was not a consecutive series. The more affected limb was defined as the limb with the greater apparent enlargement on the standardized photographs, particularly of the lower leg; the enlargement could be regional, and limb size was not taken as a measure of lipedema severity.

Data sources and verification

Data were extracted from contemporaneous sources: electronic chart entries, internal and external examination reports (including photographed copies of external reports), exports from the bioimpedance device, and dated standardized photographs. Standardized photographs (anterior, oblique, lateral, and posterior views) are stored in the chart at each visit and were treated as part of the record: visible findings (limb size and contour, skin surface, knee fat pads, sparing of the feet, and visible veins) were described from them, whereas findings that require palpation or a maneuver were taken from written entries. Every extracted item was cross-checked against its source document. Where a chart entry did not state the side of a condition, the result of the Godet and Stemmer signs, or the presence and side of knee crepitus, this was supplied retrospectively by the treating physician from recollection, not retrieved from contemporaneous records; other findings not recorded at the time of care are reported as not recorded. Stage, type, and perimetry were derived retrospectively from the dated photographs. Age and anthropometry are given at the first evaluation.

Clinical diagnosis and classification

Lipedema had been diagnosed clinically by the treating vascular surgeon; the charts recorded a working diagnosis without itemized criteria. For this report, the consensus features (disproportionate subcutaneous fat of the lower limbs, sparing of the feet, pain, tenderness or discomfort, and easy bruising) [2,7,8,28] were sought in the records and photographs and are reported for each patient. Symptoms, when recorded, had been scored with the Brazilian lipedema symptom questionnaire (QuASiL) [29]. Because the S2k guideline

requires pain [7], whereas the United States standard of care and the Delphi consensus also accept discomfort or tissue that is not always painful [2,8], patients without recorded pain were retained and identified. Pain is not universal in lipedema: in a Brazilian population survey, 9.7% of the women who met the questionnaire criterion for lipedema did not report leg pain [3]. The QuASiL also scores tenderness to touch or pressure, a feeling of pressure or tension, heaviness, and easy bruising, so that a patient who denies pain may still report the discomfort that the consensus definitions accept. Pain or tenderness was recorded in four patients (on examination in Cases 1, 4, and 5, and as self-rated pain in Case 2); in Case 6, the pain item was not recorded, but the QuASiL total was 85 of a possible 150; only Case 3 reported no pain. Type (I to V, by distribution) and morphological stage (1 to 3) were classified according to the type and stage classification described by Buck and Herbst and in the United States standard of care [8,30], from the standardized photographs by the first author and verified independently by a second author, with agreement in all patients; in Cases 2 and 4, the morphological stage recorded at registration was used. Stage 4 (lipolymphedema) was not assigned, so that coexisting lymphedema, diagnosed clinically in four patients, is reported separately from the morphological stage.

Local condition and lymphovenous work-up

For each patient, we recorded the coexisting condition and its side; its timing relative to the asymmetric worsening, as documented in the history; the Godet and Stemmer signs and any edema recorded on examination; and, where they had been performed, venous duplex findings, lymphatic assessment (lymphoscintigraphy or a documented clinical diagnosis of lymphedema), cross-sectional imaging, and histology; and medications with potential to cause edema or with hormonal activity, screened against a published list of edema-inducing drugs [16]. Because the series is retrospective, these examinations had been requested in routine care according to the clinical presentation, when their result could change management, not by a study protocol, and not every examination had been performed in every patient; they were performed at internal and external services with their routine protocols. Original images of the imaging examinations could be retrieved for three patients (Cases 2, 4, and 5). In Case 1, the subcutaneous ultrasound and the venous duplex are available only as written reports, and Cases 3 and 6 had no imaging examination of the affected limb on file; for these three patients, the supporting images are the standardized photographs, in anterior, posterior, and lateral views.

Subcutaneous ultrasound

Where available, tissue thickness had been measured at the anterior thigh, lateral leg, pre-tibial region, and supramalleolar region, the sites described in our previous ultrasound study [31]. The reports' own labels were retained: one service reported a single "dermal thickness" in millimeters, a label retained from the reports although values of up to 43.9 mm correspond to the skin and subcutaneous tissue rather than to the dermis alone, so the structure measured is uncertain; another reported dermis and subcutaneous tissue separately in centimeters, together with a descriptive conclusion.

Segmental bioimpedance

Per-limb fat percentages were obtained with segmental bioimpedance (BC-601; Tanita Corporation, Tokyo, Japan). Because bioimpedance is not recommended for body-composition estimation when hydration is abnormal [32], it was used descriptively. The side-to-side difference in the arms, which were not affected by the local conditions, served as an internal reference for side-related measurement effects.

Photogrammetric perimetry

Circumferences at six levels per limb (proximal, mid, and distal thigh; proximal, mid, and distal lower leg) were estimated from calibrated standardized frontal photographs by converting segment width to circumference under a circular cross-section assumption. The photographs were calibrated with the standardized reference used in the clinic, a half A4 sheet (14.85 cm) placed between the feet, in all six patients. Because the true cross-section of the limb is not circular, circumferences and volumes derived from frontal width under a circular assumption may be overestimated or underestimated, and absolute values are not comparable between patients; agreement between the scale references verifies the scale, not the calculated circumferences. The measurements describe the external contour at each level and do not identify which tissue or structure is enlarged; only interlimb differences within each patient are interpreted. Circumference differences are rounded to 0.5 cm and are reported to document a visibly evident difference, not as precise measurements. Limb edges were adjusted manually under magnification at most levels; levels with manual edge placement or low-confidence detection are identified. Because the method is unvalidated, relies on a single frontal view, and measures total girth rather than any specific tissue, it was used only to compare the two limbs of the same patient within the same photograph. Because both limbs share the scale, viewing angle, and shape assumption, errors common to both largely cancel in this comparison; a difference in cross-sectional shape between the limbs, for example from edema, would not cancel. The method was not validated against tape measurement, and the lateral views were not used for measurement. Segmental volumes of the thigh and lower leg were estimated from these circumferences by the truncated-cone method, between the proximal and distal measurement levels of each segment (20-80% of the hip-to-knee and knee-to-ankle distances), using the vertical distances between levels on the calibrated image; the knee region and the foot were not included. Because the volumes derive from the same circumferences, they add

no independent information; they are reported as interlimb percentage differences, with approximate absolute values. All six levels are reported, paired with bioimpedance from the same visit where available. To give context to the selection, the frontal photographs in the center's photographic archive were also screened automatically with the same software and without manual adjustment; an asymmetry alert was recorded when the estimated circumference of the proximal or mid lower leg differed between the limbs by 8% or more, a pragmatic threshold that was not derived from validation data. This screening was not used to select or measure the cases, and the alert rate describes how often an unvalidated automated measurement flagged an interlimb difference; it is not a prevalence of asymmetry.

Magnetic resonance measurement

In Case 2, the leg magnetic resonance study had included both legs in the same axial field of view, and its exported images (which do not carry the pixel spacing) were used to compare the subcutaneous compartment of the two legs. In every axial slice of the two non-fat-suppressed series, each leg was segmented automatically by intensity thresholding, and the subcutaneous compartment was defined as the tissue between the skin and the outer contour of the muscle and bone; its cross-sectional area and median radial thickness (72 radii) were measured in pixels. Because both legs share the same slice and pixel size, only left-to-right ratios are reported. Slices at the level of the knee, where the bone marrow could not be separated from the subcutaneous fat, were excluded, and the segmentation was checked visually. On these sequences, fat and fluid have similar signal, so the measurement describes the whole subcutaneous compartment and does not separate fat from edema. These measurements were made for this report and are not part of the radiology report.

Analysis

Analysis was descriptive. No statistical test of laterality was performed because patients were selected for the coexistence of asymmetry and a unilateral condition; agreement between the side of the condition and the more affected side is partly a consequence of selection [33].

Use of artificial intelligence

A large language model (Claude; Anthropic, San Francisco, CA, USA) was used to assist with language editing, cross-checking of extracted data against source documents, verification of references, drafting of the descriptions of the standardized photographs, and writing of the image-measurement scripts. The authors reviewed and verified all data, descriptions, and references and take full responsibility for the content.

Results

In the automated screening of the photographic archive (2,170 patients), a frontal photograph was found for 1,606, and both lower legs could be measured in 1,233, of whom 317 (25.7%) triggered the asymmetry alert. Patient characteristics are shown in Table *1*; the affected limb was the right in two patients and the left in four. The diagnostic work-up is summarized in Table *2*, the timing and nature of the local condition in Table *3*, and the perimetry and bioimpedance findings in Tables *4*-*6* and Figure *1*. Complete case descriptions, with dates where recorded, are provided in the Appendix.

Case	Age (years)	BMI (kg/m2)	Morphological stage	Source of stage	Type	Pain (examination; self-rating)	Affected side	Coexisting condition
1	64	25.2	2	Photographs	III	Tenderness present	Right	Varicose vein disease after two operations; red patch recorded as possible Klippel-Trénaunay syndrome (unconfirmed)
2	25	28.2	1	Registration record	III	Recorded as painless; self-rated pain 8/10	Left	Remote knee injury (2014); segmental great and small saphenous reflux; leg and foot edema on MRI
3	38	27.3	1 to 2	Photographs	III	Not recorded on examination; self-rated pain 0/10	Left	Tibial fracture at 18 years with prolonged immobilization; May-Thurner syndrome with iliac-vein stent
4	44	31.1	1	Registration record	III	Mild tenderness at first visit, absent later	Left	Clinically diagnosed lymphedema after an infected left foot injury with erysipelas; ultrasound edema greater on the left
5	39	27.5	2	Photographs	III	Tender subcutaneous fat; thigh pain	Right	Pelvic-inguinal lymphatic abnormality (MRI suggestive of angiolymphatic malformation); inguinal lymph node lesion favoring angiomyomatous hamartoma (immunohistochemistry)
6	54	35.9	2 to 3	Photographs	III	Not recorded (QuASiL total score 85; pain item not recorded)	Left	Left knee chondromalacia (knee crepitus greater on the left) and pes anserinus tendinitis; genu valgum on photographs; also recorded: fat nodules at the medial aspect of both knees; three previous varicose vein operations (side not recorded)

TABLE 1: Patient characteristics at first evaluation

BMI: body mass index; MRI: magnetic resonance imaging; QuASiL: Questionário de Avaliação Sintomática do Lipedema (lipedema symptom assessment questionnaire). Morphological stage 1-3 and type I-V according to published descriptions [8,30]; stage 4 (lipolymphedema) was not assigned. Stage and type from photographs were classified retrospectively by one author and verified by a second, with agreement.

Case	Godet sign	Stemmer sign	Edema on examination	Venous duplex	Lymphatic assessment	Other imaging/histology	Subcutaneous ultrasound (affected vs. contralateral)
1	Neg	Neg	Not recorded	Deep system competent; post-surgical right GSV; bilateral varicose veins, exuberant on the right; right AASV reflux (2025)	Not performed	None	Dermal thickness greater at all four sites (thigh 16.5 vs. 11.2 mm; pre-tibial 16.0 vs 11.1 mm), suggestive of lipedema
2	NR	NR	Left, recorded as "+"	Left GSV and SSV segmental reflux; collateral reflux in both limbs; deep system competent; May-Thurner syndrome investigated elsewhere by phlebography, no stent	External lymphoscintigraphy (recorded in chart): anomalous right popliteal uptake; external diagnosis of lymphedema	MRI: diffuse subcutaneous edema of left leg and foot; small knee effusion; left/right subcutaneous compartment area 1.25 (both legs imaged)	Not available
3	Neg	NR	Left, recorded as "+" (2022)	External ultrasound diagnosis of May-Thurner syndrome; left common iliac vein stent	Not performed; working diagnosis of left lymphedema (2022)	Contralateral (right) knee MRI (2016): patellar chondral fissures, infrapatellar fat pad edema, quadriceps and patellar tendinopathy; histology of resected deep endometriosis (2020)	Not available
4	Neg	Neg	Recorded, side not specified	Bilateral saphenofemoral and GSV reflux; SSV and perforators competent; deep system competent; bilateral ablation (2025)	Clinical diagnosis of lymphedema (compression since 2010); no lymphoscintigraphy	None	Subcutaneous tissue greater at three of four sites (thigh 1.5 vs. 1.3 cm; lateral leg 1.1 vs. 0.7 cm; supramalleolar 1.2 vs. 0.9 cm); pre-tibial site discordant between stored image and report; subcutaneous edema in both legs, more evident on the left
5	Neg	Neg	Right (2020)	No deep or superficial reflux; bilateral superficial varicosities	Lymphoscintigraphy: patent pathways, delayed drainage in both limbs, no significant dermal backflow; bilateral lymphedema listed as past history (2020); lymphangio-MRI (2022): right iliac lymphatic ectasia, drainage less efficient on the right	Thigh MRI: subcutaneous edema, no mass; PET/CT: right limb edema; pelvic MRI: right lymphatic ectasia; node IHC favoring angiomyomatous hamartoma	Dermal thickness greater at thigh (43.9 vs. 19.8 mm) and lateral leg; near-symmetric pre-tibially (12.7 vs. 12.4 mm)
6	Neg	Neg	Not recorded	Not available (three previous varicose vein operations)	Not performed	None	Not available

TABLE 2: Diagnostic work-up as documented in the records

AASV, anterior accessory saphenous vein; GSV, great saphenous vein; IHC, immunohistochemistry; MRI, magnetic resonance imaging; Neg, negative; NR, not recorded; PET/CT, positron emission tomography/computed tomography; SSV, small saphenous vein. Quotations are literal English translations of the Portuguese reports and chart entries. "Dermal thickness" is the label used in the reports; its values suggest skin plus subcutaneous tissue, and the structure measured is uncertain. In Case 3 the Godet sign was recorded in chart shorthand as "godet −". Examinations had been requested in routine care as clinically indicated, not by a study protocol; "not performed" and "none" mean that no such examination is on file, and "not available" that no report could be retrieved.

Case	Coexisting condition	Recorded sequence	Standardized photographs	Documented nature of the asymmetric excess	Local inflammatory or infectious features recorded	Potential edemagenic or hormonal exposures
1	Varicose vein disease; suspected Klippel-Trénaunay syndrome	Not dated; previously worse on the right, recent left-sided worsening	Slightly larger right limb, most at the calf; lobular fat over the medial right knee; right-sided varicose veins; mildly dimpled posterior thighs; feet spared	Greater tissue thickness (composition not characterized)	Red, painful spot on right leg (2022)	None recorded (simvastatin; pentoxifylline for 30 days)
2	Remote knee injury; saphenous reflux	Knee injury (2014), then acute left-limb swelling (2024), persistent	Larger left lower leg; fuller left ankle and foot dorsum; mild dimpling of the thighs; no knee fat pads	Subcutaneous edema (MRI)	None recorded (MRI: edema of prepatellar and lateral knee fat)	Injectable hormonal contraceptive (six years); regular ibuprofen
3	Tibial fracture; May-Thurner syndrome with stent; left-sided erysipelas	Fracture at 18 years, then left ankle edema, worse in recent years, “always only on the left”	Larger left calf; medial knee fat pads and dimpled thighs bilaterally; feet spared	Edema (clinical; working diagnosis of lymphedema)	History of erysipelas	Hormonal contraceptive and semaglutide (2022); gestrinone
4	Lymphedema after infected left foot injury; left knee chondromalacia listed	Legs never normal, with bruising; marked worsening after injury and infection, swelling greater on the left	Larger left lower leg and ankle; medial knee fat pads and dimpled thighs bilaterally; horizontal skin indentations on both legs (consistent with compression garments)	Subcutaneous edema, left greater than right (ultrasound)	Limbs described as inflamed; history of erysipelas	Levothyroxine; semaglutide, later tirzepatide
5	Pelvic-inguinal lymphatic abnormality; inguinal hamartoma	Right swelling from the day after an infected caesarean (2019); lymphatic abnormality first imaged four months later; lymphaticovenous anastomosis in the right leg (before 2022) improved leg but not thigh edema	Markedly larger right thigh; slightly larger right lower leg; lobular, dimpled skin over both thighs; medial knee fat pads bilaterally; feet spared	Subcutaneous edema with septal thickening (MRI; PET/CT)	Erythema and livedo of the thigh; subcutaneous gas foci treated as infection	Prednisone (stopped 2020); levonorgestrel intrauterine device; previous spironolactone
6	Left knee chondromalacia and pes anserinus tendinitis	Not dated	Larger left limb, most below the knee, with a large medial subgenicular fat pad extending into the upper calf; knees in contact with feet apart, consistent with genu valgum; nodular skin over both thighs and knees; medial knee fat pads bilaterally; feet largely spared	Not characterized (no imaging)	None recorded (pes anserinus tendinitis listed among possible triggers, examination findings and side not stated in the original chart entry)	Levothyroxine; melatonin; at the visit fluoxetine was prescribed and semaglutide noted in the plan

TABLE 3: Timing, photographic appearance, and nature of the coexisting condition, and potential confounders

MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computed tomography. Sequences are as recorded in the history; onset of lipedema itself was not dated in any patient.

Case	Affected side	Photograph	Thigh, proximal	Thigh, mid	Thigh, distal	Lower leg, proximal	Lower leg, mid	Lower leg, distal
1	Right	Feb 2022	+2.5†	−0.5†	+3.5†	+5.0†	+1.5†	+1.5†
2	Left	Feb 2025	0.0†	−2.0†	−0.5†	+2.5†	+3.5†	+5.5†
3	Left	Mar 2024	−1.5†	−3.0†	−0.5†	+2.0†	+3.5†	+1.0*†
4	Left	Aug 2024	−1.0†	+1.0†	+1.0†	0.0†	+2.0†	+2.5†
5	Right	Sep 2020	+4.0†	+5.5†	+8.0†	<0.5†	+0.5†	+2.0†
6	Left	Feb 2022	+4.0*†	+5.0*†	+2.0†	+5.5†	+7.0†	+2.5†

TABLE 4: Photogrammetric circumference difference between the affected and contralateral limb at six levels (cm)

Affected minus contralateral circumference, in cm, rounded to 0.5 cm; negative values indicate a larger contralateral limb. *Low-confidence edge detection. †Edge placed manually on at least one side. Circumferences were estimated from a single calibrated frontal photograph assuming a circular cross-section; they reflect total girth, not a specific tissue.

Case	Affected side	Thigh, proximal (%)	Thigh, mid (%)	Thigh, distal (%)	Lower leg, proximal (%)	Lower leg, mid (%)	Lower leg, distal (%)
1	Right	4	1	8	14	6	5
2	Left	0	3	2	7	11	25
3	Left	3	6	1	5	11	4
4	Left	2	2	3	0	8	12
5	Right	6	11	18	1	2	10
6	Left	5	7	3	9	14	9

TABLE 5: Absolute percentage circumference difference between the affected and contralateral limb at six levels

Absolute difference relative to the contralateral limb, from the same measurements as Table 4; the direction of each difference is given in Table 4.

Case	Affected side	Thigh volume difference (%)	Lower-leg volume difference (%)	Thigh + lower-leg volume, affected (L)	Thigh + lower-leg volume, contralateral (L)	Thigh + lower-leg volume difference (%)	Bioimpedance date	Leg fat, affected (%)	Leg fat, contralateral (%)	Leg fat difference (points)	Arm fat difference (points)
1	Right	+4	+18	6.8	6.3	+7	Feb 2022	38.8	39.9	−1.1	−0.6
2	Left	−6	+21	6.3	6.3	+1	Feb 2025	30.5	37.6	−7.1	+0.8
3	Left	−5	+16	5.6	5.5	+0.4	Mar 2024	35.5	39.3	−3.8	+1.0
4	Left	+2	+11	6.0	5.8	+4	Aug 2024	35.9	40.3	−4.4	−0.8
5	Right	+22	+8	7.2	6.0	+19	Jul 2020	37.7	42.7	−5.0	−0.7
6	Left	+11	+24	19.0	16.6	+15	Feb 2022	41.0	42.5	−1.5	+0.1

TABLE 6: Estimated segmental volumes and segmental bioimpedance

Volumes were estimated by the truncated-cone method between the proximal and distal levels of the thigh and of the lower leg (knee region and foot excluded); differences are affected minus contralateral relative to the contralateral limb; absolute volumes are approximate (image scale from a half A4 sheet placed between the feet; may be overestimated or underestimated, and not comparable between patients). Bioimpedance (BC-601; Tanita Corporation, Tokyo, Japan) was obtained on the day of photography except in Case 5 (eight weeks earlier), whose bioimpedance was obtained on the day a steroid-masked subcutaneous infection was suspected and prednisone was withdrawn, and whose photograph was taken during a premenstrual swelling episode with right lower-limb edema on examination. In Case 6, the device timestamp reads the day before the visit; the results were entered in the chart note of that visit, the day of photography. Fat differences are affected-side minus contralateral fat percentage, in percentage points.

L: liters



FIGURE 1: Standardized frontal photographs of the six patients with photogrammetric circumferences (cm) at six levels per limb (blue, right; magenta, left) and the estimated thigh and lower-leg volume of each limb

Panels A to F show Cases 1 to 6; each panel header gives the affected side and the coexisting condition. Photographs were taken in February 2022 (Case 1), February 2025 (Case 2), March 2024 (Case 3), August 2024 (Case 4), September 2020 (Case 5), and February 2022 (Case 6). Circumferences were estimated from the calibrated image assuming a circular cross-section; they reflect total girth, are approximate, and are used only to compare the two limbs of the same patient (Table 4). Identifying features have been removed.

Case 1

A 64-year-old woman evaluated in February 2022 reported painful, swollen legs, previously worse on the right and recently worsening on the left. She had undergone two varicose vein operations. A red patch on the right lower limb was recorded as a hypothesis of Klippel-Trénaunay syndrome; no limb overgrowth was recorded, and the syndrome was not confirmed by imaging or genetic testing. Right-predominant varicose veins, tender lipedematous fat, and negative Godet and Stemmer signs were recorded. Duplex showed a competent deep system and a post-surgical right great saphenous vein; ultrasound thickness was greater on the right at all four sites and was reported as suggestive of lipedema. During conservative management directed at lipedema, her symptom score (QuASiL) fell from 90 to 48; symptoms recurred by April 2025, when an incompetent right anterior accessory saphenous vein was ablated.

Case 2

A 25-year-old woman presented with persistent left lower-limb swelling that had begun about 10 months earlier, and reported a left knee injury 10 years before. Duplex showed segmental left great and small saphenous reflux, collateral reflux in both limbs, and a competent deep system; May-Thurner compression had been investigated elsewhere by phlebography, without stenting; magnetic resonance imaging, which included both legs, showed diffuse subcutaneous edema of the left leg and foot (Figure *2A*, *2B*, *2D*). An external lymphoscintigraphy recorded in the chart showed anomalous right popliteal uptake, and

lymphedema had been diagnosed elsewhere. Examination recorded left-limb edema and positive vitropressure, and the lipedema was recorded as painless and as “asymmetric (unilateral)”; the Godet and Stemmer signs were not recorded. Stage 1 was recorded at registration. She had used an injectable hormonal contraceptive for six years and took ibuprofen regularly.

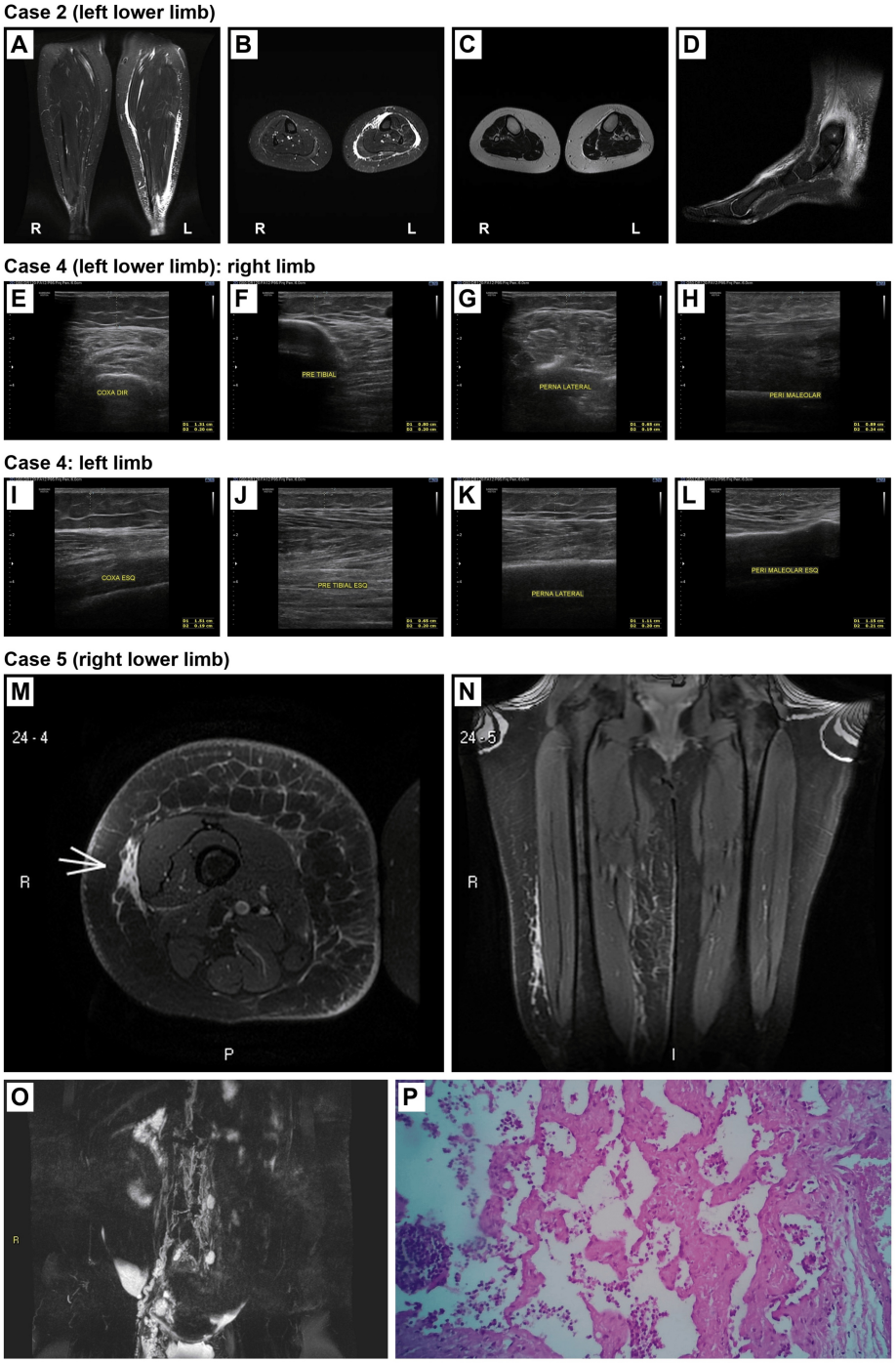


FIGURE 2: Imaging in Cases 2, 4, and 5 and histology in Case 5

Case 2 (A to D; magnetic resonance imaging, January 2024; both legs in the field of view in A to C): (A) coronal and (B) axial short-tau inversion recovery images showing diffuse, circumferential subcutaneous edema of the left leg with perifascial fluid and no edema in the right leg; (C) axial image without fat suppression, on which fat and fluid have similar signal, showing the larger left subcutaneous compartment; (D) sagittal fluid-sensitive image of the left foot with subcutaneous edema of the dorsum. Case 4 (E to L; subcutaneous ultrasound, April 2024, linear 3 to 12 MHz probe): right limb (E to H) and left limb (I to L) at the thigh (E, I), pre-tibial (F, J), lateral leg (G, K), and supramalleolar (H, L) sites; calipers: subcutaneous (D1) and dermal (D2) thickness. The subcutaneous layer was thicker on the left at the thigh, lateral leg, and supramalleolar sites; at the pre-tibial site the stored images (F, J) do not match the written report, and this site is treated as discordant (values in the text). Case 5 (M to P): (M) axial and (N) coronal magnetic resonance images of the thighs (August 2020) showing subcutaneous edema with thickened fibroadipose septa in the right thigh (arrow in M); no mass was identified. (O) Coronal lymphangio-magnetic resonance image of the abdomen and pelvis (April 2022); the right iliac lymphatic network was reported

as ectatic and tortuous. (P) Photomicrograph of the right inguinal lymph node lesion (hematoxylin and eosin) showing lymphatic channels within dense connective tissue; immunohistochemistry favored an angiomyomatous hamartoma. Panels A to L are images exported from the imaging services' archives, modified only by resizing and cropping of identifiers and empty margins; R and L follow the radiological convention, and the on-screen labels in E to L (in Portuguese) are the sonographer's. Panels M to O are key images selected by the reporting radiologists; viewer annotations and identifying information were removed.

Case 3

A 38-year-old woman evaluated in March 2024 had had left ankle edema since a left tibial fracture treated with six months of immobilization at 18 years of age, markedly worse in recent years. A left common iliac vein stent had been placed for May-Thurner syndrome in 2022, improving the leg but not the ankle. In August 2022, left lower-limb edema was recorded with a working diagnosis of lymphedema; lymphoscintigraphy was not performed. She had a history of left-sided erysipelas, had undergone surgery for deep endometriosis (2020), and had used hormonal agents. Magnetic resonance imaging of the contralateral (right) knee in 2016 had shown superficial patellar chondral fissures, edema of the infrapatellar fat pad, and quadriceps and patellar tendinopathy. Examination recorded asymmetric lipedema, a negative Godet sign, and positive vitropressure; she reported no pain.

Case 4

A 44-year-old woman evaluated in March 2024 reported that her legs had never been normal, with bruising, and that they worsened markedly after an infected foot injury followed by erysipelas, with swelling greater on the left, the side of the injury. Lymphedema had been diagnosed, and she had worn compression since 2010. Left knee chondromalacia was listed among possible triggers. Duplex showed bilateral great saphenous reflux with a competent deep system, treated by bilateral ablation in 2025. Subcutaneous ultrasound (Figure *2E*-*2L*) showed greater thickness on the left at three of the four sites (thigh, lateral leg, and supramalleolar); at the pre-tibial site, the stored image (0.65 cm on the left versus 0.80 cm on the right; Figure *2F*, *2J*) did not match the report (1.1 versus 0.8 cm), and this site is treated as discordant. The radiologist reported subcutaneous edema in both legs, more evident on the left. Stage 1 was recorded at registration, and the Godet and Stemmer signs were negative. Across seven assessments to January 2026, during incretin-based therapy, the left leg consistently had the lower bioimpedance fat percentage (by 3.1 to 6.5 percentage points).

Case 5

A 39-year-old woman evaluated in July 2020 had right lower-limb swelling since the day after an infected caesarean delivery in 2019. Pelvic magnetic resonance imaging showed right pelvic lymphatic ectasia with inguinal lymphadenopathy, later described as suggestive of an angiolymphatic malformation, and lymphoscintigraphy showed delayed drainage in both limbs. During antibiotic treatment for a suspected steroid-masked subcutaneous infection, thigh magnetic resonance imaging showed subcutaneous edema without a mass (Figure *2M*, *2N*). Lymphangio-magnetic resonance imaging in April 2022 showed ectasia and tortuosity of the right iliac lymphatic network, with edema around the right iliac vessels and less efficient drainage on the right than on the left (Figure *2O*); its indication recorded lymphatic edema of the right thigh and a previous lymphaticovenous anastomosis in the right leg that had improved the leg but not the thigh edema. A dermatology note listed “bilateral lymphedema” in her past history. The Godet and Stemmer signs were negative, and duplex showed no reflux; ultrasound thickness was greater on the right at the thigh and was reported as suggestive of lipedema. A right inguinal lymph node lesion was favored on immunohistochemistry to be an angiomyomatous hamartoma (Figure *2P*). She had also received prednisone and had a levonorgestrel intrauterine device. Right-limb enlargement was still recorded in November 2020, and no follow-up at our center after December 2020 was recorded.

Case 6

A 54-year-old woman was seen once, in February 2022. She had undergone three varicose vein operations, reported varicose veins in her mother, grandmother, and aunts, and had Hashimoto thyroiditis treated with levothyroxine. She reported chondromalacia of the left knee, and chondromalacia and left pes anserinus tendinitis were listed among possible triggers. Examination showed fat nodules at the medial aspect of both knees, knee crepitus on movement that was markedly greater on the left, and negative Godet and Stemmer signs. Standardized photographs showed a larger left lower limb, most marked below the knee, where a large medial subgenicular fat pad extended into the upper calf and accounted for much of the apparent enlargement of the lower leg, and the knees in contact with the feet apart, consistent with genu valgum. No venous duplex, lymphatic assessment, or subcutaneous ultrasound was available, and no follow-up visit was recorded.

Findings across patients

The condition of the more affected limb was venous in Cases 1 to 3 (varicose vein disease, saphenous reflux, and iliac-vein obstruction); venous reflux in Case 4 was bilateral and did not lateralize, and Case 5 had no

reflux. A lymphatic abnormality was documented on the affected side by imaging in Case 5 and by a clinical working diagnosis in Case 3; in Case 2, the side of the external lymphedema diagnosis was not recorded, and the lymphoscintigraphic anomaly was contralateral; and in Case 4, the clinically diagnosed lymphedema affected the left limb. The history placed a limb injury before the asymmetric worsening in Cases 2 to 4 (about 10 years before in Case 2); in Case 5, swelling began the day after an infected caesarean delivery, and in Cases 1 and 6, the chronology was not recorded (Table *3*). In Case 6, the condition was left knee chondromalacia with pes anserinus tendinitis; she had undergone three varicose vein operations, and no venous or lymphatic assessment was available.

Edema was recorded on examination in Cases 2 to 5 (on the affected side in Cases 2, 3, and 5; side not specified in Case 4). Magnetic resonance imaging of both legs in Case 2 (10 months before evaluation) and of both thighs in Case 5, and the descriptive ultrasound report in Case 4, reported subcutaneous edema in the affected limb. In Case 2 the left subcutaneous compartment was larger than the right in every measured axial slice of both series (50 slices; median area ratio 1.25 in each series, rising from 1.10 to 1.11 in the proximal third of the leg to 1.37 to 1.38 in the distal third; median thickness ratio 1.07 and 1.12), whereas the muscle and bone compartment differed by 4% to 5% (Figure *2C*); fat and fluid could not be separated on these sequences. The thickness-ultrasound reports in Cases 1 and 5 measured greater thickness on the affected side and concluded that the measurements were suggestive of lipedema, without describing tissue composition.

On the standardized photographs, the affected limb, or its lower leg, was visibly larger in all six patients (Figure *1*; posterior and lateral views of Cases 1, 3, and 6, the patients without diagnostic images, in Figure *3*); dimpled or lobular skin was visible in all six, and medial knee fat pads in five (bilateral in four; right only in Case 1) (Table *3*, Appendix). On perimetry, the mid-lower-leg circumference was greater on the affected side in all six patients (by 0.5-7.0 cm), and the maximal difference was at the lower leg in Cases 1 to 4 and 6 and at the distal thigh in Case 5 (+8.0 cm; Tables *4*-*6*, Figure *1*). The estimated volume of the measured lower-leg segment was larger on the affected side in all six patients (by 8-24%), and the combined thigh and lower-leg volume in four (by 4-19%); in Cases 2 and 3, the larger contralateral thigh offset the larger affected lower leg (difference ≤1%). In Case 6, the medial subgenicular fat pad contributed to the lower-leg measurements. The contralateral thigh was larger at all three thigh levels in Case 3 (by 0.5-3.0 cm), at two levels in Case 2 (by 0.5 and 2.0 cm), and at a single level in Cases 1 and 4 (by 0.5 and 1.0 cm). At the same visit (eight weeks earlier in Case 5), the affected leg returned a lower bioimpedance fat percentage than the contralateral leg in all six patients. In Cases 2 to 5, the difference (3.8-7.1 percentage points) was several times the side-to-side difference in the arms (≤1.0 point); in Cases 1 and 6, it was small (1.1 and 1.5 points), and in Case 1, it was similar to that in the arms (0.6 point), with the left arm and left leg being fattier at all five of her assessments.



FIGURE 3: Standardized posterior and lateral photographs of Cases 1, 3, and 6

Case 1 (A to C; affected limb, right): posterior (A), right lateral (B), and left lateral (C) views. Case 3 (D to F; affected limb, left): posterior (D), right lateral (E), and left lateral (F) views. Case 6 (G to I; affected limb, left): posterior (G), right lateral (H), and left lateral (I) views. These are the three patients for whom no diagnostic image is available; the photographs were taken at the same visits as the frontal photographs in Figure 1 (February 2022, March 2024, and February 2022). In the posterior views the patient's left is on the left of the image (L, R). The photographs are original chart photographs, modified only by cropping above the waist and resizing; no artificial intelligence was used. They document the visible interlimb difference and the clinical features of lipedema described in the text and in Table 3 and are not diagnostic of the coexisting condition.

Discussion

In six women with lipedema and clinically asymmetric lower limbs, the more affected limb carried a venous, lymphatic, post-traumatic, or articular condition. Where magnetic resonance imaging or a descriptive

ultrasound report was available, subcutaneous edema was reported in the affected limb. We interpret these as lipedema with a superimposed unilateral process rather than as lymphedema alone, although lymphedema or lymphatic edema had been diagnosed clinically in four patients and could not be excluded in any. This is the situation the Delphi consensus anticipates when it allows asymmetry "in the presence of comorbidities" [2], and that a review of lower-limb edema describes, for bilateral but asymmetric swelling, as a unilateral cause superimposed on a systemic background [16]. A previously published case of initially unilateral lipedema, which arose in a limb with a previous deep venous thrombosis, is consistent with this pattern [12]. In Case 6, the left limb, on the side of the chondromalacia, was larger at every perimetry level, most in the lower leg; on the photographs, much of this corresponded to a large medial fat pad below the knee, the perimetry describing the external contour without identifying which structure enlarged, and the photographs were consistent with genu valgum. Knee crepitus was markedly greater on the left. The case is compatible with two non-exclusive explanations: local articular inflammation amplifying lipedema, or regional adipose distribution associated with altered limb alignment (genu valgum) [34]; the available data cannot establish the direction of this relationship, and, with class II obesity, no knee imaging, no dated onset of the knee condition, no venous or lymphatic assessment, and no follow-up, this case cannot distinguish them and is illustrative only.

The first implication is diagnostic. Asymmetry should neither exclude lipedema nor be attributed to lipedema alone; it should prompt a search for, and characterization of, a superimposed condition. Clinical signs are imperfect guides: the Stemmer sign has limited specificity for lymphedema [35], classic signs of lymphedema predict lymphoscintigraphic lymphedema poorly, venous obstruction being their most common cause in patients without lymphedema [36], and the Delphi consensus states that pitting edema is generally absent in lipedema-affected tissue "in the absence of comorbid conditions" [2]. Lymphoscintigraphy does not settle the question either, because abnormalities are frequent in lipedema itself [15]. In our patients, venous duplex and soft-tissue imaging were the most informative, and we suggest that asymmetric lipedema be investigated with bilateral duplex and subcutaneous imaging, adding lymphoscintigraphy when lymphatic disease is suspected.

The second implication concerns measurement. In every patient, the affected limb, whose lower-leg contour was larger, returned the lower bioimpedance fat percentage. This dissociation is consistent with a superimposed conductive fluid load: women with lymphedema have higher body water and a lower bioimpedance fat percentage than women with lipedema [37], and bioimpedance is not recommended for body-composition estimation when hydration is abnormal [32]. The direction of the error is predictable: the device estimates fat-free mass from electrical impedance, assuming a constant hydration of the fat-free tissue, and derives fat as the remainder; an excess of conductive fluid in one limb lowers its impedance, which the algorithm attributes to lean tissue, so the fat percentage of that limb falls [32]. The lower value in the affected leg is therefore not offered as a measurement of fat, but as a sign of a fluid load. The arm comparison adds a safeguard: in four patients the leg difference was several times the arm difference, supporting a limb-specific effect, whereas in Cases 1 and 6 the difference was small, and in Case 1 of similar magnitude to that in the arms (1.1 versus 0.6 points), possibly reflecting a side-related measurement effect. A lower segmental fat percentage in a larger limb should therefore not be read as less adipose tissue, and bioimpedance cannot establish or exclude an adipose asymmetry.

The observations bear on, but cannot test, the hypothesis that local stasis and inflammation amplify lipedema (Figure *4*). Three findings are consistent with it. First, in three patients the history placed a limb injury before the asymmetric worsening, although by about 10 years in Case 2; temporality is the one criterion considered essential for causal inference [38]. In Case 2, however, the decade between the knee injury and the swelling means that the injury can be at most a remote predisposing factor: the swelling began abruptly about 10 months before evaluation, an emergency duplex at onset was recorded as normal, and a complete duplex the same month documented segmental saphenous reflux, with subcutaneous edema of the leg and foot on magnetic resonance imaging; the proximate trigger of that episode was not identified. Second, each affected limb carried a plausible source of stasis or inflammation: venous reflux or obstruction, lymphatic abnormality, fracture with prolonged immobilization, infection, or degenerative knee disease. Lymphatic abnormalities are frequent after lower-limb cellulitis [39], venous obstruction can cause secondary lymphedema [40], and soft-tissue trauma is followed by an inflammatory response that has been proposed to drive local adipogenesis [41]. Third, the step from stasis to fat is experimentally plausible. In a mouse model, lymphatic fluid stasis doubled subcutaneous fat thickness in association with a marked inflammatory infiltrate [24]; adipogenic gene expression followed the gradient of stasis [42]; inflammation preceded adipocyte maturation, and blocking it inhibited fat accumulation [25]; and in human lymphedema, adipocytes are larger in the affected than in the contralateral limb [43]. Lipedema tissue already carries the macrophage, endothelial, and permeability abnormalities that such a stimulus could act upon [18,20,21,23].

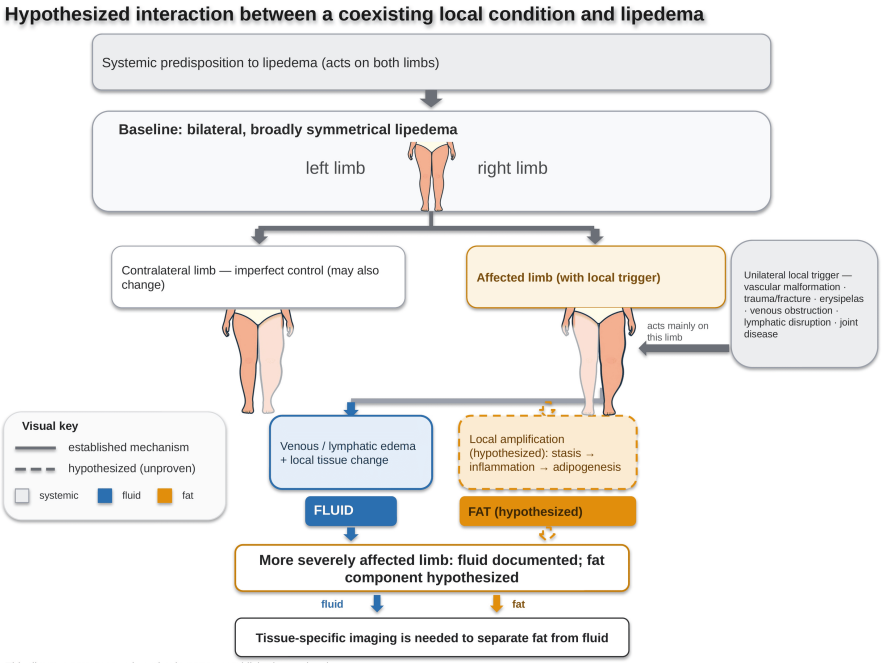


FIGURE 4: Schematic of the hypothesized interaction between a coexisting unilateral condition and lipedema

A systemic predisposition underlies bilateral, broadly symmetrical lipedema. A unilateral condition (vascular malformation, trauma or fracture, infection such as erysipelas, venous obstruction, lymphatic disruption, or joint disease) acts mainly on one limb; the contralateral limb is an imperfect control, because systemic factors act on both limbs and it may also change. Solid arrows indicate the documented pathway, in which venous or lymphatic edema and local tissue change enlarge the limb; this was the component identified in the present patients. Dashed arrows indicate the hypothesized, unproven pathway of local amplification through hypoxia, inflammation, and adipogenesis. Tissue-specific imaging is required to separate fluid from fat. The diagram represents a hypothesis, not an established causal pathway.

Image credit: diagram created by the authors in Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA); the schematic body illustration was generated by the authors with a text-to-image model (Z-Image-Turbo; Tongyi-MAI, Alibaba Group, Hangzhou, China), and the asymmetric version was derived from it by geometric widening of one leg; in the two lower panels the same asymmetric figure is shown twice, with the limb under discussion in full color and the other limb faded. It does not depict any patient.

Our data do not, however, show that the local condition increased lipedema fat. Where the soft tissue was imaged, the reports described edema in the affected limb, although the thickness-ultrasound reports in Cases 1 and 5 described the thicker side as suggestive of lipedema and no method quantified fat and fluid separately (in Case 2 the larger left subcutaneous compartment on magnetic resonance imaging could not be partitioned into fat and fluid); moreover, fat accumulating in a limb with lymphatic stasis could equally be regarded as lymphedema-associated adipose tissue rather than amplified lipedema [43]. Other observations point the other way: lipedema has been characterized as a lipodystrophy rather than a consequence of venous or lymphatic insufficiency [44], inflammatory mediators such as interleukin-6 can limit adipose deposition in experimental lymphedema [45], and in unilateral erysipelas lymphatic drainage is frequently impaired in the unaffected limb as well, which weakens the contralateral limb as a control [46]; in Case 2 the lymphoscintigraphic anomaly recorded in the right popliteal region shows that her contralateral limb was not a clean control either, and in Case 3, moreover, the contralateral (right) knee had shown chondropathy with infrapatellar fat pad edema on earlier magnetic resonance imaging, and her right thigh was the larger at all three levels. A test of the hypothesis would require prospective, bilateral, tissue-specific measurement, such as ultrasound echotexture or magnetic resonance fat-water imaging, in women with lipedema before and after a unilateral insult, together with an assessment of whether treating the local condition reduces the interlimb difference. In Case 4, the bioimpedance difference narrowed after bilateral saphenous ablation (from 4.4 to 6.5 points before ablation to 3.1 to 3.2 points after it) but widened again to 4.1 points by January 2026; because the ablated reflux was bilateral and weight and medication changed concurrently, this does not bear on the effect of treating a lateralized condition. In Case 5, a lymphaticovenous anastomosis was reported to have improved leg but not thigh edema, but no measurements before and after it were available.

Where part of the enlargement is due to a treatable venous or lymphatic condition, liposuction would not address that condition, and a cause-directed approach, treating the coexisting condition first, appears

appropriate, in line with the priority given to conservative treatment by the Brazilian consensus and with reports of successful non-surgical management [28,47]; after liposuction, reliance on conservative therapy is reduced but often persists [48-50].

This study has substantial limitations. It is a small, retrospective, purposively selected sample from a single center, and because the patients were selected for asymmetry and a unilateral condition, the observations that suggested the hypothesis cannot be used to confirm it [33]; the series shows that the pattern occurs and how it can be investigated, not how often it occurs. Where the chart did not state it, the side of the erysipelas in Case 3 and of the condition in Cases 4 and 6, the Godet and Stemmer signs in Case 4, and knee crepitus in Case 6 were supplied by the treating physician from recollection; such recall may be biased toward agreement with the visibly larger limb, although in Case 4 the ultrasound report independently placed the subcutaneous edema predominantly on the left, and in Case 3 the tibial fracture and the iliac-vein stent were documented on the left. Documentation was incomplete: the Godet sign was not recorded in one patient and the Stemmer sign in two; lymphoscintigraphy had been performed in two patients; a venous duplex report was unavailable in Case 3, in whom only the external diagnosis of May-Thurner syndrome was recorded; and no duplex had been performed in Case 6, subcutaneous ultrasound was unavailable in three, and follow-up was short or absent in several patients; Case 6 had a single recorded visit, no venous or lymphatic assessment, and class II obesity. Easy bruising, vitropressure, and pain were not recorded systematically: one patient (Case 3) reported no pain, another (Case 2) was recorded as painless despite self-rated pain, and pain was not recorded in Case 6; Case 3 would not meet the S2k definition [7], and Case 6 cannot be verified against it, although only 40% of the patients in the original Mayo Clinic series complained of pain [51]. In Case 6, with class II obesity, bioimpedance showed lower fat percentages in the legs than in the trunk and arms, so lower-limb disproportion rested on the photographs. Stage and type were classified retrospectively from photographs in most patients, by one author with verification by a second, and in Case 2 the chart recorded the lipedema as unilateral, so bilateral involvement rests on the photographic classification. Original diagnostic images could be retrieved for three patients (Cases 2, 4, and 5; Figure *2*); in Case 1 only the written ultrasound report was available, and Cases 3 and 6 had no imaging of the affected limb, so in these three patients the asymmetry rests on the clinical record and the standardized photographs (Figures *1*, *3*). The magnetic resonance measurement in Case 2 was automated, made on exported images without absolute scale, and could not distinguish fat from fluid. Perimetry was derived from single frontal photographs with an unvalidated method; edges were placed manually at most levels, three levels were of low confidence, and bioimpedance is confounded by tissue water. Several patients had used drugs with hormonal activity or with potential to cause edema (hormonal contraceptives, gestrinone, corticosteroids, a nonsteroidal anti-inflammatory drug, and incretin-based therapy; Table *3*). They were recorded at the visits and screened against a list of edema-inducing drugs; as systemic exposures, they act on both limbs and would not by themselves produce a one-sided difference, but drug-related fluid retention could be expressed more in a limb with impaired venous or lymphatic drainage and would then add to the asymmetry, and they may have changed absolute limb volume and bioimpedance values. Finally, visible findings were described from the photographs without blinded or independent assessment. The automated screening of the archive flagged about a quarter of the patients, but its median interlimb difference across all of them (5.3%) was close to the differences recorded in the present cases, so the alert rate cannot be read as a prevalence; how often lipedema is clinically asymmetric, and how often asymmetry occurs without a local condition, should be studied prospectively with validated measurement.

Conclusions

In six women with lipedema, clinical asymmetry coincided with a venous, lymphatic, post-traumatic, or articular condition in the more affected limb; where magnetic resonance imaging or a descriptive ultrasound report was available, subcutaneous edema was reported in that limb. Asymmetry should prompt a lymphovenous work-up rather than exclusion of lipedema, and a lower bioimpedance fat percentage in the larger limb should not be read as less fat, because it may reflect a superimposed fluid load. Whether local stasis and inflammation also amplify the adipose component of lipedema is a plausible hypothesis that these observations raise but cannot answer, and that warrants prospective, tissue-specific study.

Appendices

Complete case descriptions are available as a supplementary appendix at https://drive.google.com/file/d/1B0YEO7GENpXdRElb2tmEOvODpJ7qJ1oj/view.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Alexandre C. Amato

Acquisition, analysis, or interpretation of data: Alexandre C. Amato, Juliana L. Amato, Daniel A. Benitti, Keller S. Santos

Drafting of the manuscript: Alexandre C. Amato

Critical review of the manuscript for important intellectual content: Alexandre C. Amato, Juliana L. Amato, Daniel A. Benitti, Keller S. Santos

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Research Ethics Committee of the University Hospital of the University of São Paulo issued approval 00880826.1.0000.0076. The study complied with the Declaration of Helsinki. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

This study was not preregistered. De-identified data are available from the corresponding author on reasonable request, subject to ethics committee approval.

References

1. Buso G, Depairon M, Tomson D, Raffoul W, Vettor R, Mazzolai L: Lipedema: a call to action!. Obesity (Silver Spring). 2019, 27:1567-76. 10.1002/oby.22597
2. Kruppa P, Crescenzi R, Faerber G, et al.: Lipedema World Alliance Delphi consensus-based position paper on the definition and management of lipedema: results from the 2023 Lipedema World Congress in Potsdam. Nat Commun. 2026, 17:427. 10.1038/s41467-025-68232-z
3. Amato AC, Amato FC, Amato JL, Benitti DA: Lipedema prevalence and risk factors in Brazil . J Vasc Bras. 2022, 21:e20210198. 10.1590/1677-5449.202101981
4. Kruppa P, Georgiou I, Biermann N, Prantl L, Klein-Weigel P, Ghods M: Lipedema-pathogenesis, diagnosis, and treatment options. Dtsch Arztebl Int. 2020, 117:396-403. 10.3238/arztebl.2020.0396
5. Warren Peled A, Kappos EA: Lipedema: diagnostic and management challenges . Int J Womens Health. 2016, 8:389-95. 10.2147/IJWH.S106227
6. Allen EV, Hines EA Jr: Vascular clinics. X. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic edema. Proc Staff Meet Mayo Clin. 1940, 15:184-7. 10.1016/S0025-6196(25)37697-4
7. Faerber G, Cornely M, Daubert C, et al.: S2k guideline lipedema. J Dtsch Dermatol Ges. 2024, 22:1303-15. 10.1111/ddg.15513
8. Herbst KL, Kahn LA, Iker E, et al.: Standard of care for lipedema in the United States . Phlebology. 2021, 36:779-96. 10.1177/02683555211015887
9. Keith L, Seo C, Wahi MM, et al.: Proposed framework for research case definitions of lipedema . Lymphat Res Biol. 2024, 22:93-105. 10.1089/lrb.2023.0062
10. Forner-Cordero I, Perez-Pomares MV, Forner A, Ponce-Garrido AB, Munoz-Langa J: Prevalence of clinical manifestations and orthopedic alterations in patients with lipedema: a prospective cohort study. Lymphology. 2021, 54:170-81. 10.2458/lymph.4838
11. Aday AW, Donahue PM, Garza M, et al.: National survey of patient symptoms and therapies among 707 women with a lipedema phenotype in the United States. Vasc Med. 2024, 29:36-41. 10.1177/1358863X231202769
12. Alshomer F, Lee SJ, Kim Y, Hong DW, Pak CJ, Suh HP, Hong JP: Lipedema associated with skin hypoperfusion and ulceration: soft tissue debulking improving skin perfusion. Arch Plast Surg. 2024, 51:311-6. 10.1055/a-2181-8469
13. Amato ACM, Markus DV, Santos RV: Lipedema associated with obesity, lymphedema, and venous insufficiency: a case report [Article in Portuguese]. Diagn Tratamento. 2020, 25:4-8.
14. Luta X, Buso G, Porceddu E, Psychogyiou R, Keller S, Mazzolai L: Clinical characteristics, comorbidities, and correlation with advanced lipedema stages: a retrospective study from a Swiss referral centre. PLoS One. 2025, 20:e0319099. 10.1371/journal.pone.0319099
15. Forner-Cordero I, Oliván-Sasot P, Ruiz-Llorca C, Muñoz-Langa J: Lymphoscintigraphic findings in patients with lipedema. Rev Esp Med Nucl Imagen Mol (Engl Ed). 2018, 37:341-8. 10.1016/j.remn.2018.06.008
16. Gasparis AP, Kim PS, Dean SM, Khilnani NM, Labropoulos N: Diagnostic approach to lower limb edema. Phlebology. 2020, 35:650-5. 10.1177/0268355520938283
17. Forner-Cordero I, Muñoz-Langa J, Morilla-Bellido L: Building evidence for diagnosis of lipedema: using a classification and regression tree (CART) algorithm to differentiate lipedema from lymphedema patients. Int Angiol. 2025, 44:71-9. 10.23736/S0392-9590.25.05207-1
18. Wolf S, Rannikko JH, Virtakoivu R, et al.: A distinct M2 macrophage infiltrate and transcriptomic profile decisively influence adipocyte differentiation in lipedema. Front Immunol. 2022, 13:1004609. 10.3389/fimmu.2022.1004609
19. Kruppa P, Gohlke S, Łapiński K, et al.: Lipedema stage affects adipocyte hypertrophy, subcutaneous adipose tissue inflammation and interstitial fibrosis. Front Immunol. 2023, 14:1223264. 10.3389/fimmu.2023.1223264
20. Strohmeier K, Hofmann M, Jacak J, et al.: Multi-level analysis of adipose tissue reveals the relevance of perivascular subpopulations and an increased endothelial permeability in early-stage lipedema.

Biomedicines. 2022, 10:1163. 10.3390/biomedicines10051163
21. Michelini S, Greco S, Vaia N, et al.: Endothelial cell alterations in capillaries of adipose tissue from patients affected by lipedema. Obesity (Silver Spring). 2025, 33:695-708. 10.1002/oby.24244
22. Ishaq M, Bandara N, Morgan S, et al.: Key signaling networks are dysregulated in patients with the adipose tissue disorder, lipedema. Int J Obes (Lond). 2022, 46:502-14. 10.1038/s41366-021-01002-1
23. Felmerer G, Stylianaki A, Hollmén M, et al.: Increased levels of VEGF-C and macrophage infiltration in lipedema patients without changes in lymphatic vascular morphology. Sci Rep. 2020, 10:10947. 10.1038/s41598-020-67987-3
24. Zampell JC, Aschen S, Weitman ES, Yan A, Elhadad S, De Brot Andrade M, Mehrara BJ: Regulation of adipogenesis by lymphatic fluid stasis: part I. Adipogenesis, fibrosis, and inflammation. Plast Reconstr Surg. 2012, 129:825-34. 10.1097/PRS.0b013e3182450b2d
25. Cuadrado GA, de Andrade MFC, Ariga SK, de Lima TM, Souza HP: Inflammation precedes fat deposition in an experimental model of lymphedema. Lymphat Res Biol. 2021, 19:116-25. 10.1089/lrb.2020.0061
26. Riley DS, Barber MS, Kienle GS, et al.: CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017, 89:218-35. 10.1016/j.jclinepi.2017.04.026
27. Murad MH, Sultan S, Haffar S, Bazerbachi F: Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med. 2018, 23:60-3. 10.1136/bmjebm-2017-110853
28. Amato AC, Peclat AP, Kikuchi R, et al.: Brazilian consensus statement on lipedema using the Delphi methodology. J Vasc Bras. 2025, 24:e20230183. 10.1590/1677-5449.202301832
29. Amato AC, Amato FC, Benitti DA, Dos Santos RV: Translation, cultural adaptation, and validation of a lipedema symptoms questionnaire. J Vasc Bras. 2020, 19:e20200049. 10.1590/1677-5449.200049
30. Buck DW 2nd, Herbst KL: Lipedema: a relatively common disease with extremely common misconceptions . Plast Reconstr Surg Glob Open. 2016, 4:e1043. 10.1097/GOX.0000000000001043
31. Amato ACM, Saucedo DZ, Santos KDS, Benitti DA: Ultrasound criteria for lipedema diagnosis. Phlebology. 2021, 36:651-8. 10.1177/02683555211002340
32. Kyle UG, Bosaeus I, De Lorenzo AD, et al.: Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr. 2004, 23:1430-53. 10.1016/j.clnu.2004.09.012
33. Kempen JH: Appropriate use and reporting of uncontrolled case series in the medical literature . Am J Ophthalmol. 2011, 151:7-10.e1. 10.1016/j.ajo.2010.08.047
34. Amato AC: Chondromalacia in lipedema: the sarcopenic-valgus cascade that keeps getting missed . Cureus. 2025, 17:e95299. 10.7759/cureus.95299
35. Goss JA, Greene AK: Sensitivity and specificity of the Stemmer sign for lymphedema: a clinical lymphoscintigraphic study. Plast Reconstr Surg Glob Open. 2019, 7:e2295. 10.1097/GOX.0000000000002295
36. Jayaraj A, Raju S, May C, Pace N: The diagnostic unreliability of classic physical signs of lymphedema . J Vasc Surg Venous Lymphat Disord. 2019, 7:890-7. 10.1016/j.jvsv.2019.04.013
37. Stellmaker R, Thompson B, Mackie H, Koelmeyer L: Comparison of fluid and body composition measures in women with lipoedema, lymphoedema, and control participants. Clin Obes. 2024, 14:e12658. 10.1111/cob.12658
38. Fedak KM, Bernal A, Capshaw ZA, Gross S: Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol. 2015, 12:14. 10.1186/s12982-015-0037-4
39. Soo JK, Bicanic TA, Heenan S, Mortimer PS: Lymphatic abnormalities demonstrated by lymphoscintigraphy after lower limb cellulitis. Br J Dermatol. 2008, 158:1350-3. 10.1111/j.1365-2133.2007.08423.x
40. Raju S, Furrh JB 4th, Neglén P: Diagnosis and treatment of venous lymphedema . J Vasc Surg. 2012, 55:141-9. 10.1016/j.jvs.2011.07.078
41. Galea LA, Penington AJ, Morrison WA: Post-traumatic pseudolipomas--a review and postulated mechanisms of their development. J Plast Reconstr Aesthet Surg. 2009, 62:737-41. 10.1016/j.bjps.2008.12.021
42. Aschen S, Zampell JC, Elhadad S, Weitman E, De Brot Andrade M, Mehrara BJ: Regulation of adipogenesis by lymphatic fluid stasis: part II. Expression of adipose differentiation genes. Plast Reconstr Surg. 2012, 129:838-47. 10.1097/PRS.0b013e3182450b47
43. Zhang J, Hoffner M, Brorson H: Adipocytes are larger in lymphedematous extremities than in controls . J Plast Surg Hand Surg. 2022, 56:172-9. 10.1080/2000656X.2021.1953042
44. Harwood CA, Bull RH, Evans J, Mortimer PS: Lymphatic and venous function in lipoedema . Br J Dermatol. 1996, 134:1-6. 10.1046/j.1365-2133.1996.d01-741.x
45. Cuzzone DA, Weitman ES, Albano NJ, et al.: IL-6 regulates adipose deposition and homeostasis in lymphedema. Am J Physiol Heart Circ Physiol. 2014, 306:H1426-34. 10.1152/ajpheart.01019.2013
46. Damstra RJ, van Steensel MA, Boomsma JH, Nelemans P, Veraart JC: Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic study of 40 patients with unilateral erysipelas of the leg. Br J Dermatol. 2008, 158:1210-5. 10.1111/j.1365-2133.2008.08503.x
47. Amato AC, Benitti DA: Lipedema can be treated non-surgically: a report of 5 cases . Am J Case Rep. 2021, 22:e934406. 10.12659/AJCR.934406
48. Amato AC, Amato JL, Benitti D: Efficacy of liposuction in the treatment of lipedema: a meta-analysis . Cureus. 2024, 16:e55260. 10.7759/cureus.55260
49. Baumgartner A, Hueppe M, Meier-Vollrath I, Schmeller W: Improvements in patients with lipedema 4, 8 and 12 years after liposuction. Phlebology. 2021, 36:152-9. 10.1177/0268355520949775
50. Bejar-Chapa M, Rossi N, King N, Hussey MR, Winograd JM, Guastaldi FP: Liposuction as a treatment for lipedema: a scoping review. Plast Reconstr Surg Glob Open. 2024, 12:e5952. 10.1097/GOX.0000000000005952
51. Wold LE, Hines EA Jr, Allen EV: Lipedema of the legs; a syndrome characterized by fat legs and edema . Ann Intern Med. 1951, 34:1243-50. 10.7326/0003-4819-34-5-1243