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Case Report of Painful Nodules in Lipedema: Correlation between Qualitative Ultrasonographic Classification and Histological Findings

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ABSTRACT

Lipedema is a chronic and progressive condition characterized by the disproportionate accumulation of subcutaneous adipose tissue predominantly in the upper and lower limbs, sparing the trunk, hands, and feet. It affects approximately 12.3% of the female population in Brazil. Clinically diagnosed, its most common symptoms include tenderness upon palpation and spontaneous bruising. During the development of a qualitative ultrasonographic classification for lipedema, termed Lipedema Dermis and Hypodermis Classification (LDHC), an echogenic nodule was identified in the superficial hypodermis. This nodule was painful upon superficial palpation and lacked ultrasonographic features of a lipoma. The patient presented with a nodule in the distal posterior region of the right thigh and another on the distal posterior of the right arm. Given the possible differential diagnoses, including neoplasia and angiodysplasia, an ultrasound-guided biopsy was performed. Macroscopic analysis revealed an oval-shaped, reddish nodule, suggestive of blood content. Histological analysis revealed areas of steatonecrosis, hemorrhagic foci, and neoangiogenesis with irregular architecture and fragile vessel walls. Complementary analysis of the resistance index (RI) of superficial hypodermal arteries demonstrated an increased RI in the lipedema patient compared to the control. All these findings suggest that the tissue is hypoxic and characterized by chronic inflammation, supporting the hypothesis of increased subcutaneous compartment pressure in lipedema. This case report elucidates the ultrasonographic findings of nodules classified by LDHC through microscopic anatomical correlation and aids in understanding the pathophysiological mechanisms underlying

lipedema.

1. INTRODUCTION

Lipedema is characterized by the disproportionate accumulation of adipose tissue in the subcutaneous compartment of the upper and lower limbs, while sparing the feet, hands, and trunk. It affects approximately 12.3% of the female population in Brazil, although this figure may be underestimated, suggesting potential underdiagnosis [1, 2]. Diagnosis is clinical, based on patient history and physical examination, which often contributes to diagnostic delays and errors. Clinical manifestations include tenderness on palpation, non-pitting edema (negative Godet's sign), spontaneous bruising, functional limitation, and marked cosmetic changes [2, 3].

The etiology of lipedema remains uncertain; however, current evidence suggests a multifactorial origin involving genetic, hormonal, inflammatory, microvascular, and lymphatic components [4, 5]. These theories still lack robust scientific documentation, being insufficient to completely elucidate, not only the triggering factors but also the detailed pathophysiology.

Currently available clinical classifications for lipedema are divided into two categories. The first, and most widely used, is the topographic classification, which categorizes the disease according to the anatomical location affected (**Figure 1**) [2]. The second classification is based on functional severity and disease progression, considering skin texture, subcutaneous involvement, and the presence of lymphedema (**Table 1**) [6].

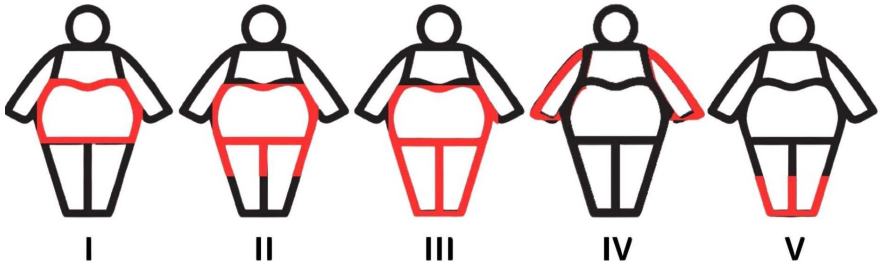


Figure 1. Anatomical classification of lipedema: Type I: hips. Type II: hips and thighs. Type III: hips, thighs, and legs. Type IV: arms. Type V: legs [2].

Table 1. Progressive functional classification (adapted) of lipedema according to clinical signs in skin, subcutaneous tissue, and lymphatic involvement.

	Skin	Subcutaneous tissue	Lymphatic Involvement
Stage 1	Smooth	Increased, Nodules	Absent
Stage 2	Irregular	Increased, Nodules	Absent
Stage 3	Skin folds	Increased, Nodules, Fibrosis	Absent
Stage 4	Skin folds	Increased, Nodules, Fibrosis	Present

Source: Adapted from Herbst, 2012 [6].

Imaging examinations for lipedema diagnosis have developed significantly in recent years, particularly to aid in differentiating it from other conditions such as obesity and lymphedema [7, 8]. The most commonly used imaging techniques include dual-energy X-ray absorptiometry (DEXA), ultrasonography (US), lymphoscintigraphy, and magnetic resonance imaging (MRI).

Recently, the US has been increasingly used for lipedema diagnosis, employing quantitative assessment of dermal and hypodermal thickness at predetermined regions of the lower limbs, with established reference values available in the literature (Table 2) [7]. Additionally, a qualitative ultrasonographic assessment method has recently been proposed, based on specific patterns observed in the dermis, dermal-hypodermal junction, and hypodermis in patients diagnosed with lipedema. This method evaluates three regions of the lower limbs, identifying four distinct patterns of architectural changes in the skin and subcutaneous tissue associated with lipedema (Table 3). This system is termed the Lipedema Dermis and Hypodermis Classification (LDHC) [9].

Table 2. Reference values for quantitative ultrasonographic diagnosis of lipedema.

TOPOGRAPHY	THICKNESS (mm)
Pre-tibial (mid-region)	Greater than 11.7
Anterior thigh (mid-distal)	Greater than 17.9
Lateral leg (mid-proximal)	Greater than 8.4
Medial leg (supramalleolar region)	Greater than 7.0

Source: Adapted from Amato *et al.*, 2021 [7].

Table 3. LDHC qualitative ultrasonographic classification.

LDHC	Architecture	Hypodermal septa	Echogenic nodules	Dermal-hypodermal junction
1	Preserved	Linear and thin Less than 50% rupture	Absent	Preserved
2	Bulging	Irregular and curved ≅ 50% rupture	Absent	Preserved
3	Bulging deep Disorganized superficial	Irregular Disruption superficial	Present	Irregular
4	"Marbled"	Irregular Branching and verticalization	Absent	Irregular ("serrated")

Source: Adapted from Vargas *et al.*, 2025 [9].

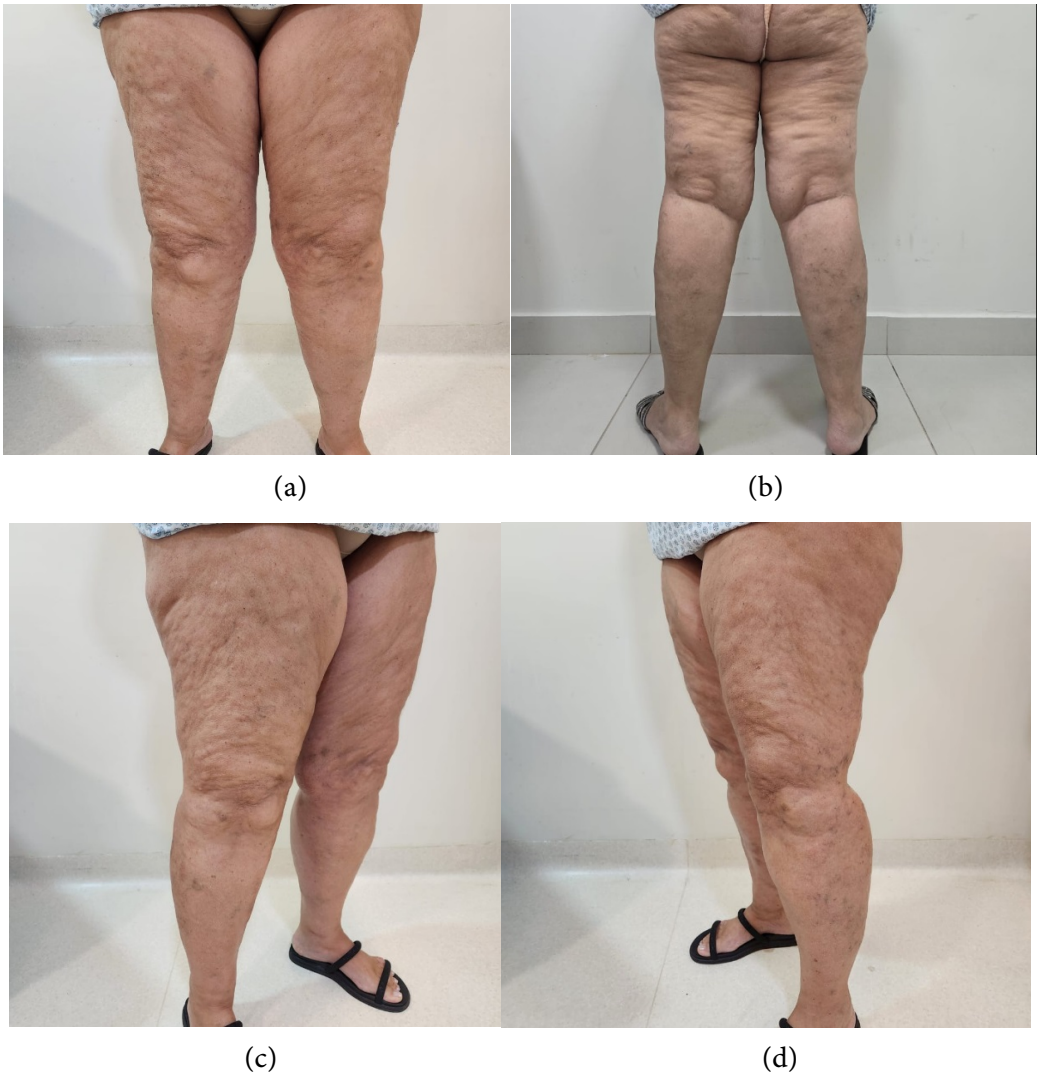
2. CASE REPORT

A 55-year-old Caucasian female reported the onset of increased thigh volume following her second pregnancy (22 years of age), without spontaneous regression. She described a progressive clinical course characterized by pain, heaviness, and fatigue in her lower limbs, associated with spontaneous bruising and edema, which worsened on hot days. She also noted cyclic exacerbation of symptoms, particularly during her menstrual period. Menarche occurred at 11 years of age, she used oral contraceptives for an unknown duration, and experienced menopause at 49 years of age (after hysterectomy due to myoma, without oophorectomy). She denied associated clinical comorbidities. Her surgical history included three phlebectomy procedures, including right-sided saphenectomy. She regularly engages in physical activity, although she currently reports difficulties with high-impact exercises due to pain and joint impairment, particularly in her knees. She denied tobacco and alcohol use and described her diet as low in fat, sugar, and refined flour.

On physical examination, she weighed 78 kg and was 1.65 m tall, with a body mass index (BMI) of 28.7 kg/m^2. Her lower limbs exhibited sparse bruising (reported as spontaneous by the patient), a CEAP (clinical, etiological, anatomical, and pathological) varicose vein classification of C1, palpable pedal and posterior tibial pulses, and negative Godet's and Stemmer's signs. Several palpable and painful subcutaneous nodules were identified. Lower limb circumference measurements are described in Table 4. Anatomically/topographically, the lipedema was classified as types II and IV, and functionally as Stage 3 (Figure 2).

Table 4. Lower limb circumference measurements.

	Right lower limb (cm)	Left lower limb (cm)
Thigh	65	65
Leg	45	44
Ankle	27	25



(a) (b)

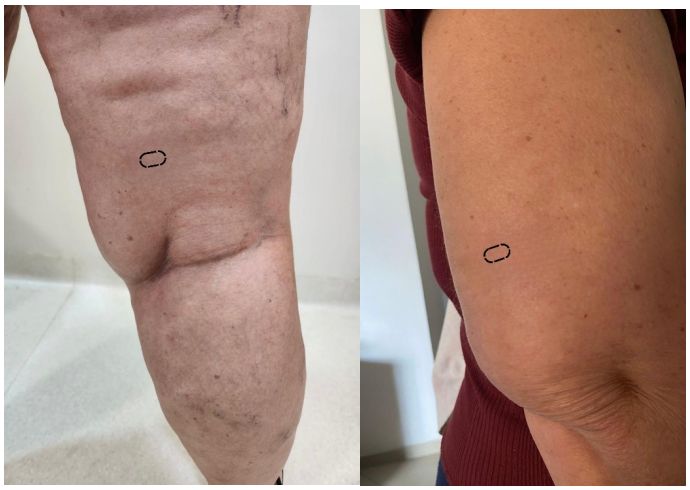
(c) (d)

Figure 2. Images of the lower limbs: (a) anterior view, (b) posterior view, (c) right lateral view, (d) left lateral view.

Current specific treatment for lipedema includes metformin 1000 mg/day, spironolactone 25 mg/day, regular physiotherapy, and manual lymphatic drainage. The patient also used elastic compression stockings (20 - 30 mmHg, 7/8 length).

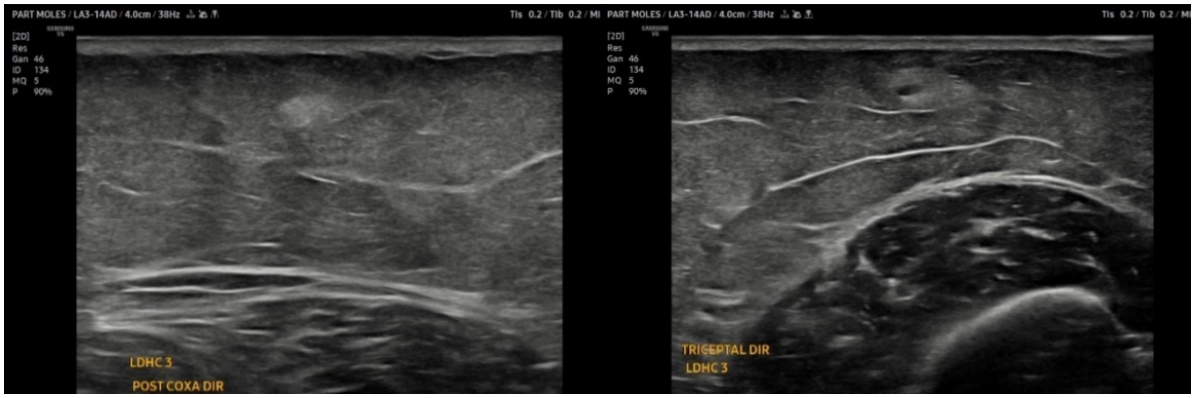
3. CASE REPORT—METHODS

Ultrasonographic assessment of the dermis and hypodermis was performed exclusively in B-mode using a high-frequency linear transducer (10 - 15 MHz) on a Samsung V6 device (Samsung Medison Co. Ltd., Republic of Korea, 2024). Images were acquired in the longitudinal plane at a minimum depth of 4 cm, revealing echogenic nodules at clinically painful points (LDHC 3). These nodules were characterized by ill-defined and irregular borders and were not consistent with lipoma. Considering potential differential diagnoses such as neoplasia and angiodysplasia, biopsy of these nodules was recommended. Consequently, ultrasound-guided preoperative markings were made at the distal posterior region of the right thigh (**Figure 3(a)**) and the distal posterior region of the right arm (**Figure 3(b)**). Ultrasonographic images of the echogenic nodules in the right thigh and right arm are presented in **Figure 4(a)** and **Figure 4(b)**, respectively. Institutional ethics approval was obtained covering imaging use and biopsy procedures.



(a) (b)

Figure 3. Representation of pre-surgical marking of the nodules in: (a) posterior right thigh, (b) posterior right arm.



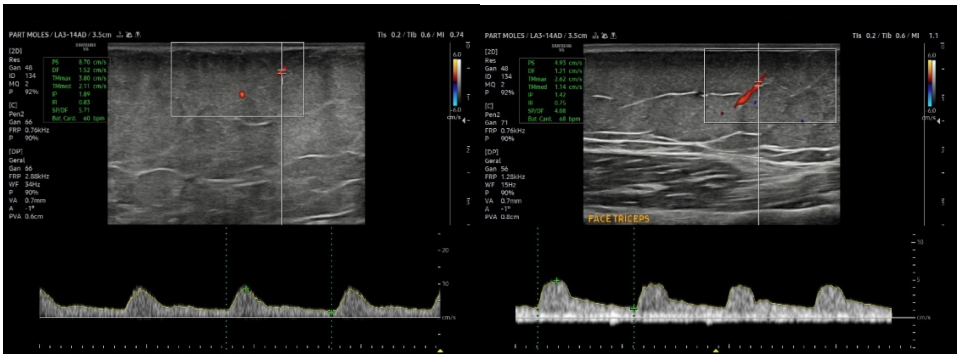
(a) (b)

Figure 4. Ultrasound images of echogenic nodules (LDHC 3) in: (a) right thigh, (b) right arm.

With biopsy indication confirmed, it was proposed to evaluate the resistance index (RI) of the superficial hypodermal artery using Doppler ultrasound at the nodule sites and compared with values obtained from the corresponding regions of an age-matched control participant. Table 5 compares data from the lipedema patient and the control case, presenting age, weight, BMI, dermal and hypodermal thickness of the right thigh and arm, and the RI of superficial hypodermal arteries in the thigh (Figure 5) and right arm (Figure 6).

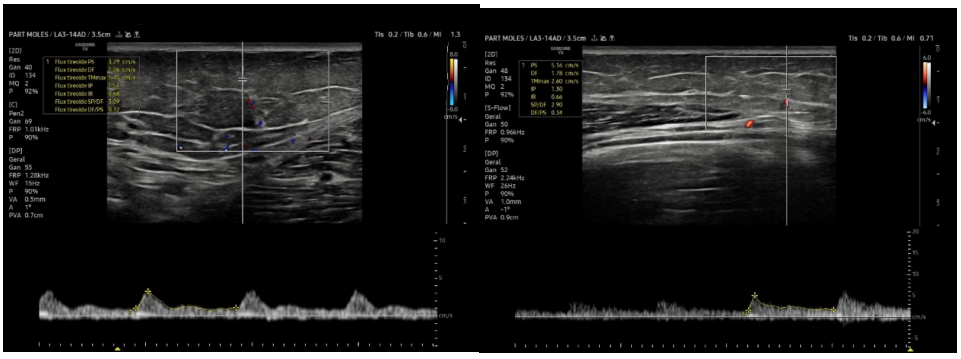
Table 5. Comparative data between the lipedema patient and control case.

	Control	Lipedema
Age (years)	29	55
Weight (kg)	59	78
BMI (kg/m^2)	23.0	28.7
Right thigh thickness (mm)	22.0	40.0
Right thigh RI	0.68	0.83
Right arm thickness (mm)	13.0	22.0
Right arm RI	0.66	0.75



(a) (b)

Figure 5. Doppler images from the lipedema patient demonstrating RI measurements of: (a) right thigh, (b) right arm.



(a) (b)

Figure 6. Doppler images from the control case demonstrating RI measurements of: (a) right thigh, (b) right arm.

Following ultrasound-guided marking of the nodules, the patient underwent local anesthesia for biopsy procedures, utilizing a fusiform technique encompassing both dermis and hypodermis. Incisions were made following Langer's lines to minimize scarring, with an average depth of 2.0 cm. The specimens were initially evaluated macroscopically and through digital dermatoscopy (Leviacam, Fotofinder Tricholab, Germany) at 20× (Figure 7 and Figure 8). Subsequently, they were fixed in 10% formalin solution and then sent to the pathology department. Samples were later processed, embedded in paraffin, sectioned at 4 μm thickness using a microtome, and stained with hematoxylin and eosin (HE).

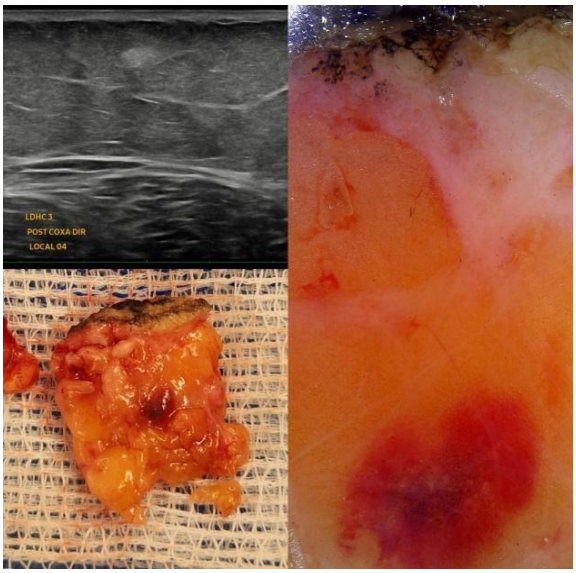


Figure 7. Posterior right thigh nodule: top left, the echogenic nodule visualized on ultrasonography (LDHC 3); bottom left, the excised surgical material; right, surgical material analyzed under 20× using dermatoscopy.

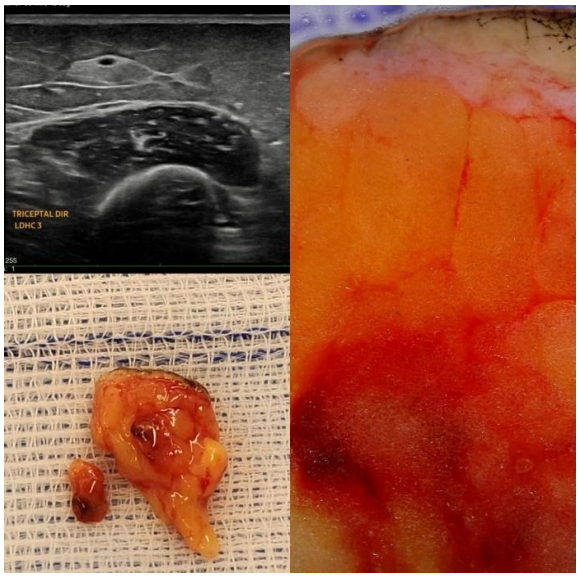


Figure 8. Posterior right arm nodule: top left, the echogenic nodule visualized on ultrasonography (LDHC 3); bottom left, the excised surgical material; right, surgical material analyzed under 20× using dermatoscopy.

Histological analysis was performed by three blinded, independent pathologists experienced in dermatopathology. The following parameters were evaluated: steatonecrosis, fibrosis, inflammatory infiltrate, hemorrhage, vascular congestion, neoangiogenesis, and vasculitis. Figure 9 shows hemorrhage areas, hemosiderin deposits, fibrous proliferation, steatonecrosis foci and granular eosinophilic content. Figure 10 demonstrates hemorrhagic extravasation and histiocytic reaction.

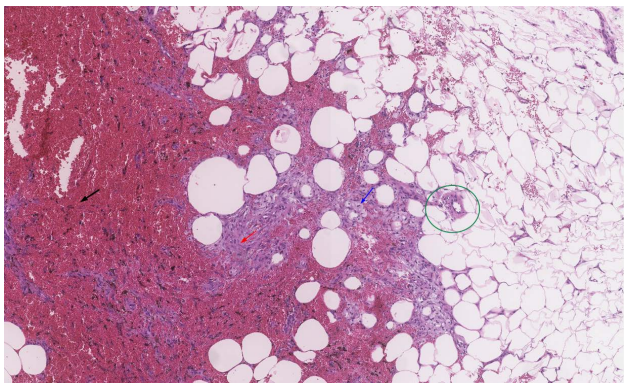


Figure 9. Optical microscopy image (100×) of the nodule from the right thigh, showing abundant representation of subcutaneous adipose tissue, identified in the central regions of adipose lobules, which is distant from fibrous septa. Hemorrhage areas and hemosiderin deposits (black arrow) are observed, interspersed with fibrous proliferation (red arrow). Steatonecrosis foci (blue arrow) are also observed, characterized by necrotic adipocytes with "ghost-like outlines" and granular eosinophilic content. No vasculitis or significant inflammatory infiltrate was observed. The epidermis and dermis show no relevant histological alterations.

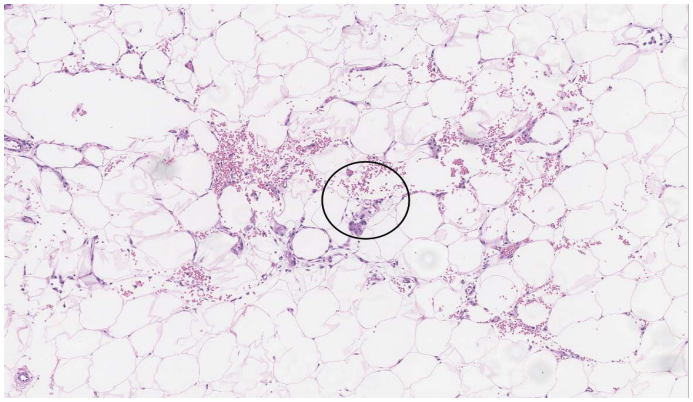


Figure 10. Optical microscopy image (200×) of the nodule from the right arm, showing the central region of adipose lobules with areas of hemorrhagic extravasation and histiocytic reaction (circle).

4. DISCUSSION

This patient's lipedema symptoms coincided with periods of high estrogenic hormonal activity, such as during her second pregnancy and worsening during her menstrual cycle, supporting the theory of a genetic predisposition coupled with cumulative estrogen exposure [10]. Symptom aggravation during phases of high estrogen load, such as menarche, oral contraceptive use, pregnancy, and menopause, may represent

a cumulative factor, acting as "memory" in adipose tissue to estrogen exposure.

The confusion of symptoms of venous insufficiency due to varicose veins with those of lipedema, beyond their coexistence [11], can result in patients undergoing surgical treatments, including saphenectomy. However, lipedema is an inflammatory disease, and surgical procedures in inflamed areas may worsen clinical symptoms rather than improve them.

The clinical treatment for lipedema is based on dietary adjustments and adapted physical exercise. Untreated patients may develop deformities and joint alterations, such as gonarthrosis [12], which hinder the full implementation of treatment, perpetuating a vicious cycle and contributing to disease progression. Currently, low-impact activities, such as water aerobics and variations, are recommended.

The presence of subcutaneous nodules in patients with lipedema is well documented; however, their ultrasonographic identification and classification as LDHC 3 is recent. This classification assesses irregularity at the dermal-hypodermal junction, architectural disorganization of the hypodermis, and the presence of focal echogenic areas; these findings suggest advanced stages of the disease [4]. Currently used classifications do not lead to therapeutic changes, nor do they allow for longitudinal follow-up. Because of its qualitative evaluation, the LDHC classification has the potential to assist in these aspects. As the ultrasonographic findings were not characteristic of lipoma or other common conditions, and in light of diagnostic uncertainties such as neoplasia and angiodysplasia, a biopsy was performed to analyze the composition of the nodules.

During the biopsy, both macroscopic examination and dermatoscopy (20×) showed that the nodules exhibited a reddish coloration within the adipose tissue, consistent with the previously identified echogenic nodule on ultrasound and suggestive of hematoma. Microscopic analysis confirmed hemorrhagic foci, irregular and fragile neovascularization, and steatonecrosis. Histological inflammatory markers were identified only in the right arm sample, such as histiocytic infiltrate, possibly related to an advanced or chronic stage of lipedema.

Steatonecrosis, observed in the central regions of the adipose lobules, may be the first direct histological evidence suggestive of increased pressure in the subcutaneous compartment, because tissues distant from capillaries are nourished by diffusion, imbibition, and osmosis. This increased pressure would result in chronic hypoxia, which could stimulate an immature neoangiogenesis (tortuous and fragile capillaries) that are prone to rupture, potentially resulting in hemorrhage, as observed in this case [13, 14]. The same increased pressure could impair venous and lymphatic drainage, contributing to edema and lymphatic involvement in advanced stages of the disease [15, 16], as well as neural compression, which may explain chronic pain [17].

Neoangiogenesis responsible for hemorrhages in the hypodermis has already been associated with spontaneous cutaneous bruising, one of the main symptoms of lipedema [13, 18]. These hemorrhages, whether in the dermis or hypodermis, recruit inflammatory cells such as mast cells and macrophages, thereby perpetuating the pro-inflammatory state and eventually leading to fibrosis. Mast cell degranulation, accompanied by the release of heparinoid compounds, contributes to a pro-hemorrhagic environment [19]. Fibrosis would result in stiffening of the skin and subcutaneous tissues, which may also be a cause of chronic pain reported by these patients [2, 20].

Echogenic nodules on ultrasound, classified as LDHC 3, present histological correlation with extravascular blood deposits (hematoma) and steatonecrosis areas. In this case report, biopsy confirmed interlobular hemorrhage and immature neovascularization, characterizing an area of "metabolic scars, resulting from adipose expansion, increased subcutaneous tissue pressure, and chronic hypoxia. Although these findings are individually nonspecific, their combination reinforces the LDHC classification as a potential "virtual biopsy", capable of obviating invasive procedures in typical cases.

All findings support the "subclinical compartment syndrome" theory, in which hypertrophy and hyperplasia of subcutaneous adipose tissue occur in a disorganized manner, leading to increased pressure within the subcutaneous compartment. This increased pressure causes hypoxia, which progresses to steatonecrosis and immature neovascularization, making it prone to rupture and bleeding, stimulating a cellular

inflammatory response that increases edema and compartmental pressure, perpetuating the cycle [15].

However, from a different standpoint, a new theory may be proposed. The process begins with hyperplasia and hypertrophy of adipose tissue, which increases the demand for oxygen supply, leading to hypoxia, which in turn results in neoangiogenesis and steatonecrosis. However, the increased compartmental pressure further promotes maladaptive angiogenesis, which is incompletely matured, predisposing to bleeding and creating a vicious cycle of ineffective ischemia–revascularization, as illustrated by Figure 11. Nevertheless, the exact sequence of events remains uncertain and requires further study.

Doppler evaluation of superficial hypodermal arteries has been previously investigated, but limited to the vessels quantification, without flow pattern or resistance index (RI) [13]. In the RI analysis by Doppler, a reduced RI was expected, secondary to vasodilation due to the chronic inflammation of lipedema. However, when compared to the control patient, the interesting finding was the opposite, increased arterial resistance in the superficial hypodermis in the lipedema patient. Although this is an isolated finding, it indirectly suggests an increased pressure in the subcutaneous compartment.

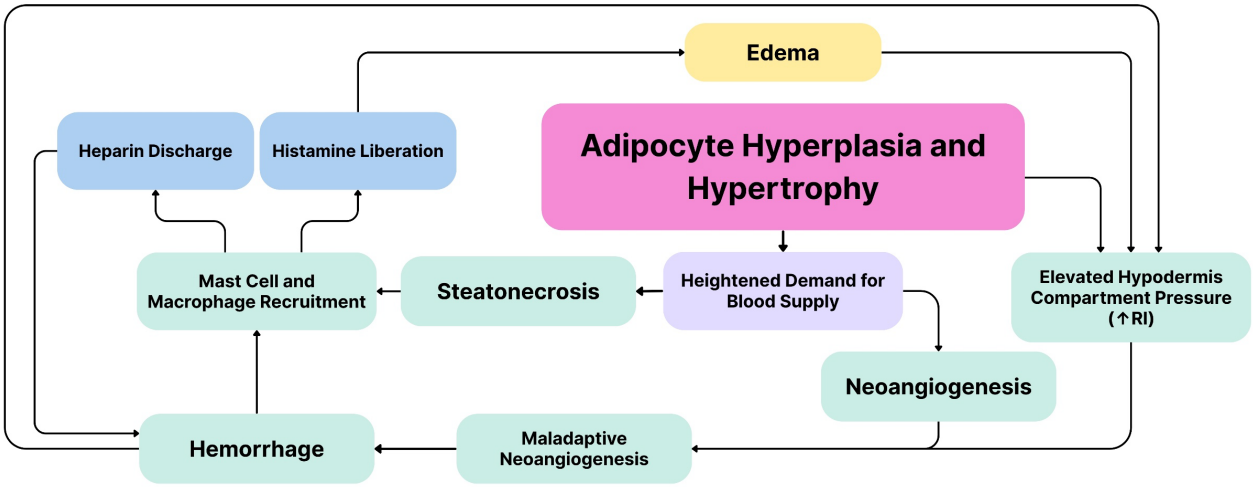


Figure 11. Pathophysiological diagram of a new proposed theory: maladaptive neoangiogenesis secondary to increased compartmental pressure. Ultrasonographic and histological findings in this study are highlighted in green boxes.

5. CONCLUSION

The findings reinforce the hormonal and genetic influences on the progression of lipedema. Although a specific gene has not yet been identified, patients appear to experience cumulative estrogenic influence throughout life. Clinical symptoms may overlap with venous manifestations, requiring careful evaluation by specialists. Lipedema can progress with orthopedic complications that limit adherence to full treatment protocols. Current classification systems lack clinical and therapeutic applicability. The US is already established as a quantitative diagnostic tool, and when combined with the LDHC qualitative classification, it suggests findings with potential diagnostic, histopathological, therapeutic, and follow-up value. Painful subcutaneous nodules classified as LDHC 3 may help differentiate lipedema from obesity, lipoma, and lymphedema. Histological analysis of these nodules revealed that LDHC 3 may be a marker of inflammation, steatonecrosis, neoangiogenesis, and hemorrhage, contributing to the understanding of lipedema's pathophysiology, although further elucidation of mechanisms is needed. Doppler-derived RI may serve as an indirect marker of elevated subcutaneous compartment pressure. These findings may guide non-invasive monitoring in future longitudinal studies, but larger samples are needed to confirm these findings and establish clinical correlation, with the goal of improving diagnosis, guiding therapeutic choices, monitoring disease progression, and fostering the development of new technologies for lipedema management.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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