Lipedema associated with obesity, lymphedema and venous insufficiency: a case report

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Abstract

Context: Lipedema, although prevalent, is an underdiagnosed morbid condition.

Case description: This article presents the case of an 80-year-old female patient with several co-morbidities who has constant painful and pruritic episodes in the lower limbs, as well as skin changes, associated with difficulty walking and bending the legs, together with the constant presence of hematomas, ecchymoses and a constant feeling of heaviness in the lower limbs.

Discussion: Lipedema is usually confused with its main differential diagnoses, such as lymphedema and obesity.

Conclusions: Knowledge of the pathophysiology and clinical features of the disease is therefore essential, so that an accurate diagnosis can be made and, in this way, appropriate treatment can be established.

Keywords: Lipedema, differential diagnosis, vascular diseases, Lymphedema, Obesity, Venous Insufficiency, epidemiology.

Introduction

Lipedema is a hereditary, chronic and progressive condition characterized by abnormal accumulation of fat in the subcutaneous tissue, mainly in the lower limbs; according to Fife et al., its prevalence is 11% in the female population.[1,2] It is a frequently underdiagnosed condition, mistaken for other morbid states such as lymphedema and obesity.[1,3] Lymphedema is characterized by interstitial accumulation of protein-rich fluid and may have a primary or secondary etiology.[4] Obesity, in turn, is defined in adults by the World Health Organization (WHO) as a body mass index (BMI) greater than 30 kg/m².[5] The coexistence of these comorbidities makes clinical diagnosis difficult, because the clinical pictures are often similar.[6,7] The diagnosis of lipedema can be challenging, especially in very early or more advanced phases, as is the case of stage IV of the disease, in which the so-called lipolymphedema occurs.[7,8] We

therefore clarify questions regarding the clinical picture of lipedema and how to distinguish it from its main differential diagnoses.[9]

Case description

This report was reviewed and approved by the Institutional Ethics Committee in July 2019, under protocol opinion 20190701.

An 80-year-old female patient presented with constant complaints of pain in the lower limbs, edema, marked difficulty walking and bending the leg, and a feeling of heaviness in the lower limbs (Figure 1). She reported restless legs and described extreme sensitivity to touch and pressure in the affected areas, as well as very frequent appearance of hematomas and ecchymoses on the lower limbs. She reported sporadic episodes of leg cramps, in addition to an intense feeling of heaviness, fatigue and swelling. She also reported a strong sensation of itching, as well as a moderate sensation of pressure and heat in the lower limbs. She stated that she had been diagnosed with lymphedema, hypertension and varicose veins in the past.

After her last pregnancy, she reported weight gain, and she had been treated for more than 20 episodes of erysipelas, the last of which had occurred more than two years earlier. Physical examination showed a preferential distribution of fat in the lower limbs, painful on palpation, lymphedema, leg ulcers, ochre dermatitis and lipodermatosclerosis. The patient reported that these conditions profoundly affect her quality of life, expressing dissatisfaction not only with the physical limitations that the condition imposes on her but also with the appearance of her legs.

She currently takes acetylsalicylic acid, atenolol, chlorthalidone, levothyroxine, amlodipine, duloxetine hydrochloride, and diosmin for the treatment of varicose veins of the lower limbs. Bone densitometry of the lumbar spine, right femur and left forearm was normal. Lymphoscintigraphy of the lower limbs (Figure 2) showed patent lymphatic pathways on the left side and partially obstructed superficial lymphatic pathways on the right side, with marked dermal backflow, without impairment of drainage time. On color duplex ultrasound of the lower-limb veins (Figure 3), the left side showed a great saphenous vein with proximal insufficiency and an incompetent saphenofemoral junction, in addition to varicose veins and absence of perforator veins. The right side showed varicose veins and segmental reflux in the great saphenous vein. The other structures were preserved.



Figure 1. An 80-year-old patient with lipolymphedema of the lower limbs, with trophic lesions on both legs. Clinical signs can be observed, such as lipodermatosclerosis, ulcerations, cutaneous hyperpigmentation, legs with an "inverted champagne bottle" appearance, cuffed ankles, as well as eczema and symmetrical involvement.[10]

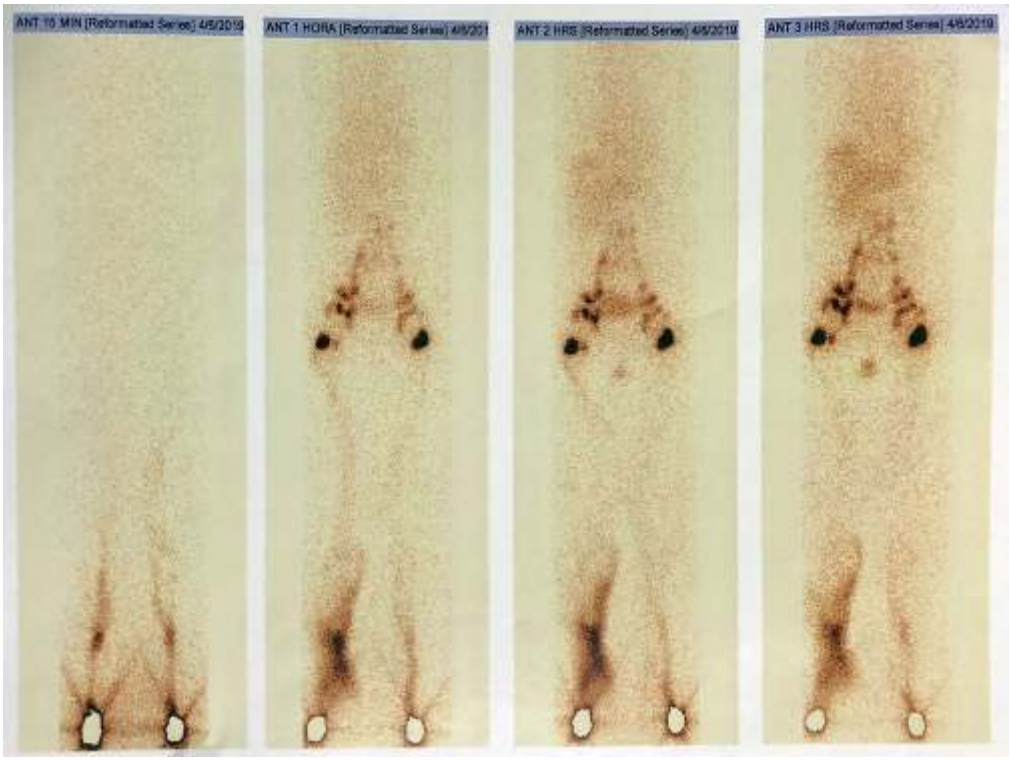


Figure 2. Lymphoscintigraphy shows partially obstructed superficial lymphatic pathways in the right lower limb, but without impairment of drainage time. The lymphatic pathways of the left lower limb were patent. Lymphoscintigraphy is the gold-standard test for the assessment of the lymphatic system, being the only test that can clearly indicate its function.[11]

Discussion

The etiology of lipedema has not been clarified. However, genetic factors are assumed to be paramount in the manifestation of the disease, given its high occurrence across different generations of the same family.[8] The patient's daughter has the same preferential distribution of fat in the lower limbs and painful symptoms, although of lower intensity.

Confusion in the diagnosis of lipedema is frequent, even when it occurs in isolation. When it is associated with other comorbidities, this confusion increases. This is partly due to physicians' lack of familiarity with the disease and partly to the absence of a specific diagnostic method, the main differential diagnoses being lymphedema, obesity and Dercum's disease.[7-9] However, when studied separately, there are significant differences between them.

Lymphedema is characterized by edema related to conditions that reduce lymphatic return. These may be primary, such as Milroy disease, or secondary, for example as a result of radiation to lymph nodes or superficial/deep skin infections.[9] The patient reports multiple episodes of erysipelas, with lymphatic involvement demonstrated by lymphoscintigraphy. In addition, lymphedema may affect the hands and the regions below the ankle, unlike lipedema, which spares them in stages I to III. Lymphedema is usually unilateral, in contrast with lipedema, which is generally symmetrical. Furthermore, lymphedema has no sex predilection, unlike lipedema, which affects mostly women, especially after major hormonal changes such as puberty and menopause.[7] Likewise, lymphatic edema is pitting and causes long-term skin changes, with a positive Stemmer sign. Lipedema, in its early stages, causes neither pitting edema nor skin changes (except in stage IV of the disease), and the Stemmer sign is negative. A useful test for differentiating these two conditions is lymphoscintigraphy, which tends to be abnormal in patients with lymphedema, unlike in patients with lipedema.[1,7] Differentiating lymphedema from lipedema becomes particularly difficult when obesity is associated with these conditions.[7,11]

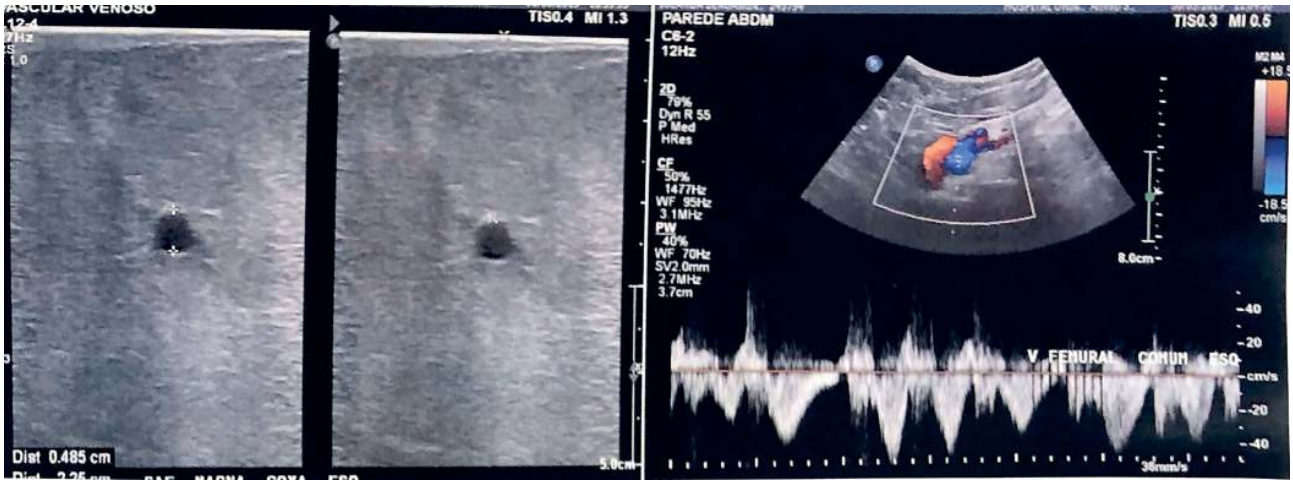


Figure 3. Venous color duplex ultrasound of the lower limbs shows a patent and competent deep venous system; patent superficial venous system, an incompetent perforator vein on the left at 16 cm from the plantar region, and segmental reflux in the great saphenous veins without dilation. Abundant adipose tissue is noted.

Diagnostic confusion between lipedema and obesity is also very common. Although obesity may have some influence on the development of lipedema, both diseases should be considered separate entities requiring individualized diagnosis.[6] Some differences between these diseases are striking. Obesity causes a generalized, painless accumulation of fat in the body. Lipedema, in contrast, has a predilection for the lower limbs and presents with painful hypersensitivity, also showing vascular changes such as capillary fragility, which results in petechiae and easy bruising. Although there are some atypical subtypes of lipedema that can cause uncharacteristic fat accumulation in the lower extremities, the disease usually spares these regions, unlike obesity.[7] In addition, lipedema is resistant to changes in diet and lifestyle. This can be best seen in patients who have undergone bariatric surgery and who, if they have lipedema, have greater difficulty losing weight in the lower limbs compared with the rest of the body.[2,6] Along with this, patients with lipedema may be wrongly classified as obese (BMI > 30) because of regional enlargement caused by lipedema.[8] According to Buck and Herbst, worsening of lipedema has been documented in patients exposed to weight-loss stressors. Other parameters can also be assessed, such as type 2 diabetes, which is very common in obese patients but shows no clinical correlation in patients with lipedema.[6]

Dercum's disease, or adiposis dolorosa, is characterized by chronic, symmetrical subcutaneous accumulation of fat in the form of nodules, together with significant pain. It is therefore an important differential diagnosis for lipedema.[7,10,12] However, there are striking differences between these conditions. The prevalence of type 2 diabetes is significantly lower in patients with lipedema than in those with Dercum's disease. Although fatigue and edema are common to both diseases, skin bruising has been shown to be much more prevalent in lipedema, owing to capillary fragility; moreover, Dercum's disease typically presents with intense pain, mainly in the abdominal region, together with shortness of breath, which is not usually observed in lipedema. Notably, the fat distribution in patients with Dercum's disease and lipedema shows some similarity, although lipedema has a lower accumulation pattern than Dercum's disease. However, Dercum's disease causes broader systemic manifestations.[13]

Although the molecular mechanisms that lead to the development of lipedema are not well understood, there are evident clinical signs and symptoms that make the diagnosis of this disease possible, and imaging studies are not even necessary.[1,6] In 1951, some authors pioneeringly proposed six diagnostic criteria. These referred to some important aspects of the disease, such as epidemiological characteristics and features specific to the patient's physical examination.[7] Over the years, the criteria underwent modifications, proposed by Bilancini et al. and by Herbst.[7,14] Currently, the main features for the correct

diagnosis of the disease are as follows: in lipedema, there is symmetrical, bilateral and progressive de - position of fat in the lower limbs, usually sparing the feet, as in the case reported. Thus, the cuff sign can be observed, defined by the "trouser-like" morphological appearance of the lower limbs, which is less evident in this case because of the intense lipodermatosclerosis. Furthermore, when lipedema is not associated with other conditions that reduce lymphatic flow, the Stemmer sign is negative; it may, however, become positive as the disease progresses, culminating in the so-called lipolymphedema, a stage clinically demonstrated by the patient.[7] In addition, the adipose tissue may feel granular on palp - ation, similar to "grains of sand", or nodular, similar to "beans in a bag", as reported in the history and found on physical examination. Together with this, the affected areas are markedly sensitive to touch and pressure, and patients bruise easily because of subdermal capillary fragility; telangiectasias may also frequently occur in the affected areas.[6]

Pain on palpation is not characteristic of lymphedema, venous insufficiency or obesity. In addition, the history of the disease shows slow progression that does not respond to diet and physical exercise[7,9] (Table 1). It is also relevant to point out that certain diets can increase inflammatory modulators in the body, thereby worsening inflammatory states already established in the body.[15,16] The association of these comorbidities is not commonly described in the literature (Table 2); few published studies have addressed the complex assessment and identification of these cases.

	Lipedema	**Obesity**	**Chronic venous insufficiency**	**Lymphedema**
Sex	Exclusively female	Male and female	Male and female	Male and female
Pain	Yes	No	Probably yes	Probably no
Edema	Non-pitting or slightly pitting	Usually no edema	Present or absent	Pitting
Physical examination findings	Stemmer sign (–) in the early phases; Stemmer sign (+) in lipolymphedema; cuff sign (+)	Stemmer sign (–)	There may be active or healed ulcers, as well as hyperpigmentation	Stemmer sign (+)
Onset	Related to major hormonal changes (e.g., pregnancy)	At any age	Primary: onset in the 2nd and 3rd decades of life; Secondary: later	Congenital; after surgical procedures; after local irradiation or after skin infection
Location	Bilateral, symmetrical	Bilateral	Unilateral or bilateral	Often unilateral

Table 1. Comparison of the most striking features of lipedema and its main differential diagnoses (the signs and symptoms presented by the patient in this case are highlighted in red).

Table 2. Results of the search in the medical databases PubMed and Google Scholar, performed on 11/23/2019

Database	**Search strategy**	**Total references retrieved**	**Total related references**	**Total references from Brazilian studies**
PubMed/ NCBI	((“obesity”[MeSH Terms] OR “obesity”[All Fields]) AND (“varicose veins”[MeSH Terms] OR (“varicose”[All Fields] OR “veins”[All Fields]) OR “varicose veins”[All Fields])) AND ((“lipedema”[MeSH Terms] OR “lipedema”[All Fields]) OR (“lymphoedema”[All Fields] OR “lymphedema”[MeSH Terms] OR “lymphedema”[All Fields]))	16	4 (all from the last century, only one still accessible for reading)	0
Google Scholar		362	0	0

Conclusion

Lipedema, although very prevalent, is a frequently underdiagnosed disease compared with other pathological states. This situation is harmful to patients, who are often only partially cared for. The need for better identification of the disease is therefore evident, as is knowledge of its progressive pathophysiological nature, in order to establish appropriate treatment that, consequently, has a positive impact on patients' lives. Distinguishing the main differential diagnoses is necessary, but occasionally these diagnoses may be identified concomitantly with lipedema. The patient in question, in addition to lipedema, had lymphedema, venous insufficiency and obesity. Initially, we should always look for a single disease that explains all the signs and symptoms presented, but occasionally we may find several associated comorbidities, especially in older patients and after long periods without an adequate diagnosis.

Declarations

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