Chapter 17
Differential Diagnosis – Lipedema

Győző Szolnoky

Introduction

Lipedema is an infrequently recognized and often neglected clinical entity that nearly always affects women. It poses a diagnostic challenge as one of the common disorders that is easily confused with lymphedema.[1-4]

Definition

Lipedema is disproportional obesity characterized by bilateral, symmetrical, biker's hosiery-shaped fatty swelling of the legs; arms are also commonly involved.[1-4] Various synonyms are found in the literature (adiposalgia, adipositas dolorosa, adipositas spongiosa, adipositas edematosa, thick leg of healthy woman, fat leg, fatty edema, lipidosis, lipomatosis dolorosa, rider's hosiery disorder, column leg, stove pipe leg, jelly leg, areal adiposity, lipohypertrophia corporis inferioris, segmental adiposity, inferior obesity). This abundance of terminology and unclear definitions have resulted in some confusion about lipedema, causing under-diagnosis and misdirected treatment.[5]

Manifestations of lipedema typically appear after puberty.[2-4] Women are affected almost exclusively. Men usually develop lipedema on the basis of hormonal disturbance; however, there is one published case report in which a healthy man was diagnosed with lipedema.[6] The general incidence of lipedema among women is reported to be as high as 11%.[2] Ten to 18% of all patients referred to lymphedema clinics are diagnosed with lipedema. It has been suggested that among all women with increased fat deposits of the lower extremities, 60% are caused by obesity, 20% by lipedema, and 20% by a combination of both.[3]

G. Szolnoky
Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

B.-B. Lee et al. (eds.), *Lymphedema*,
DOI 10.1007/978-0-85729-567-5_17,

Lipedema presumably occurs against an endocrinological and genetic background.[2,7,8] Two leading hallmarks are the frequent appearance of ecchymosis and hematomas, even after minor traumatic injuries, and spontaneous or palpation-induced pain.[1-4] Lipedema, especially in advanced stages, occurs quite frequently in association with lymphatic or venous insufficiency. The comorbidities may substantially modify the original limb shape and obscure the diagnosis.[2-4]

Clinical Diagnosis

In most cases the diagnosis of lipedema can be established by the patient's history and clinical examination.[2-4] There is no absolutely unambiguous pathognomonic diagnostic test for lipedema.

Classification

At stage I, the skin looks flat, but the subcutis is already enlarged and on palpation feels like "styrofoam balls in a plastic bag" (see Fig. 17.1). At stage II (see Fig. 17.2), walnut- to apple-sized indurations develop and the overlying skin has an irregular surface ("mattress phenomenon"). Stage III shows larger indurations and deforming-to-lobular fat deposits (see Fig. 17.3).

A classification scheme has been proposed on the basis of the location of the fat deposits: mainly buttocks (type I), buttocks to knees (type II), buttocks to ankles (type III), mainly arms (type IV), and mainly lower legs (type V).[9]

Differential Diagnosis

The most notable differential diagnosis of lipedema (see Tables 17.1–17.3) embraces obesity, various forms of lipohypertrophy and venous edema or lymphedema.

Unilateral or bilateral venous edema is a hallmark of chronic venous insufficiency. Pitting edema usually disappears or is minimal after bed rest. In contrast to lymphedema, Stemmer sign is typically negative.[2]

In obesity, the distribution of subcutaneous fat deposits is usually generalized. Simple obesity may equally affect men and women. Furthermore, the typical sparing of the feet and the pain of lipedema are lacking. Unlike lipedema, simple obesity efficiently responds to restricted diet and increased exercise. Lipedema is frequently combined with obesity and altered body structure may misdirect the clinician, resulting in an inaccurate diagnosis. Early lipedema may be associated with normal weight.[2,10]

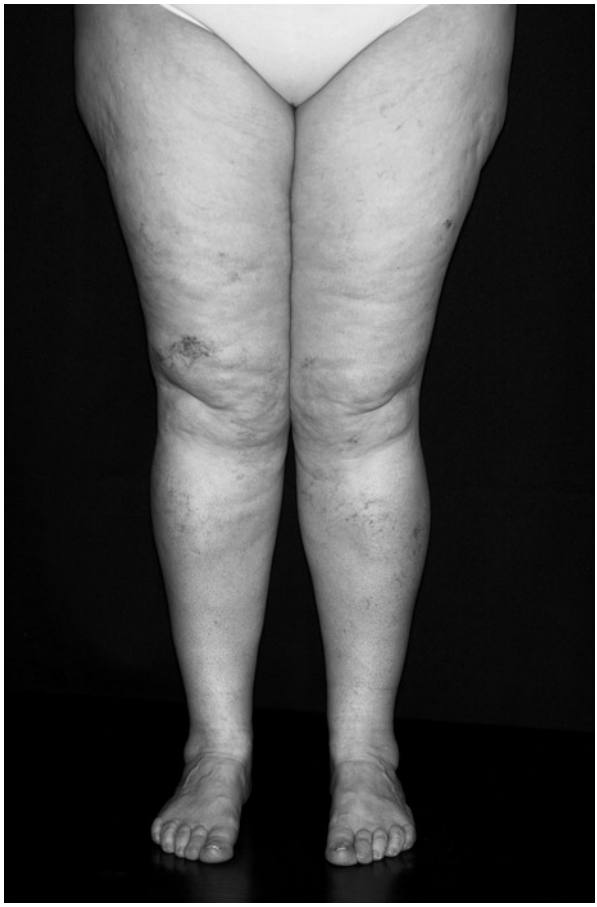

Fig. 17.1 Stage I lipedema

Lipohypertrophy is described as increased symmetrical subcutaneous fat deposits, mostly on the legs and arms in women.[11] Lipedema is preceded by lipohypertrophy. The basic difference between lipohypertrophy and lipedema resides in the absence of edema and pain in lipohypertrophy. However, there are also painful subtypes of lipohypertrophy. One widely used categorization identifies *lipomatosis indolens simplex* (multiple lipomas without relevant symptoms), *lipomatosis dolorosa* (painful fat deposition), *lipomatosis atrophicans* (accompanying fat atrophy), and *lipomatosis gigantea* (overgrowing fatty parts).

The term "lipodystrophy" is usually reserved for local damaged subcutaneous fat.[12] Acquired partial lipodystrophy is called Barraquer–Simons syndrome, in which adipose tissue loss is noted primarily in the neck, face, arms, thorax, and upper abdomen. The clinical onset is during childhood or adolescence, predominantly among women. These women are frequently subject to hirsutism, amenorrhea or polycystic ovary syndrome.

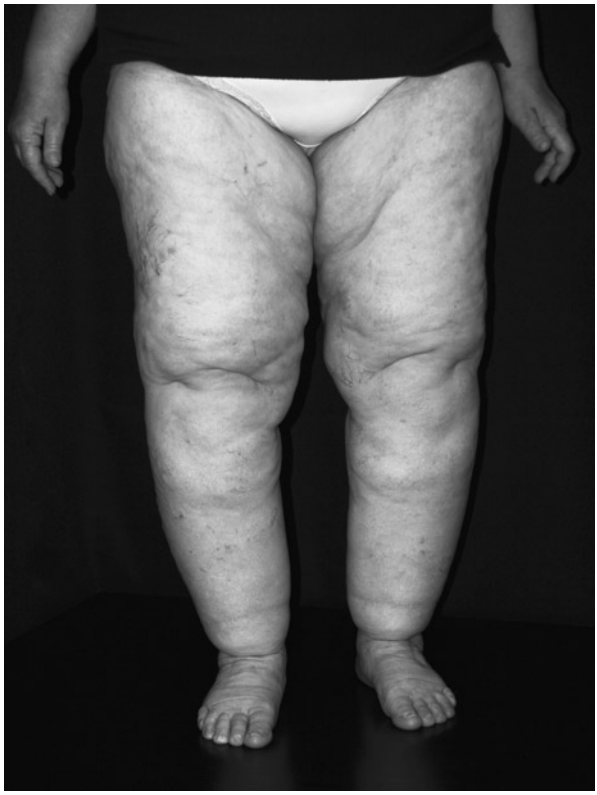

Fig. 17.2 Stage II lipedema

Dercum's disease (*lipomatosis dolorosa*) is a rare, symmetrical disorder involving the inner side of upper arms, elbows, stomach wall, buttocks, inner and outer surfaces of thighs and knees with painful subcutaneous adipose tissue deposits.[13] Severe hyperalgesia is triggered by even light pressure. It is 5–30 times more frequent in women than in men and usually results in a number of psychosocial problems that may partially be attributed to the context of chronic pain syndrome. Other characteristic symptoms are swollen hands and fingers with accompanying paresthesias, numbness, joint stiffness, dryness of eyes and mouth, and teleangiectasia with increased fragility of vessels causing ecchymoses. It may first occur in menopause and is not associated with edema.

Benign symmetric lipomatosis (Madelung's disease or Launois–Bensaude syndrome) is a rare, benign disorder of unknown etiology.[14,15] This syndrome is characterized by multiple, symmetric, non-encapsulated fatty accumulation diffusely involving the neck and upper trunk areas. It uncommonly involves the lower limbs and lower trunk. Madelung's disease can be divided into three major forms according to location: type I (neck), type II (shoulders, interscapular region, and upper arms), and type III (lower trunk). In other classifications, there are proximal (neck, shoulders, scapular region), central (backs, thighs), and distal (knees, hands, and

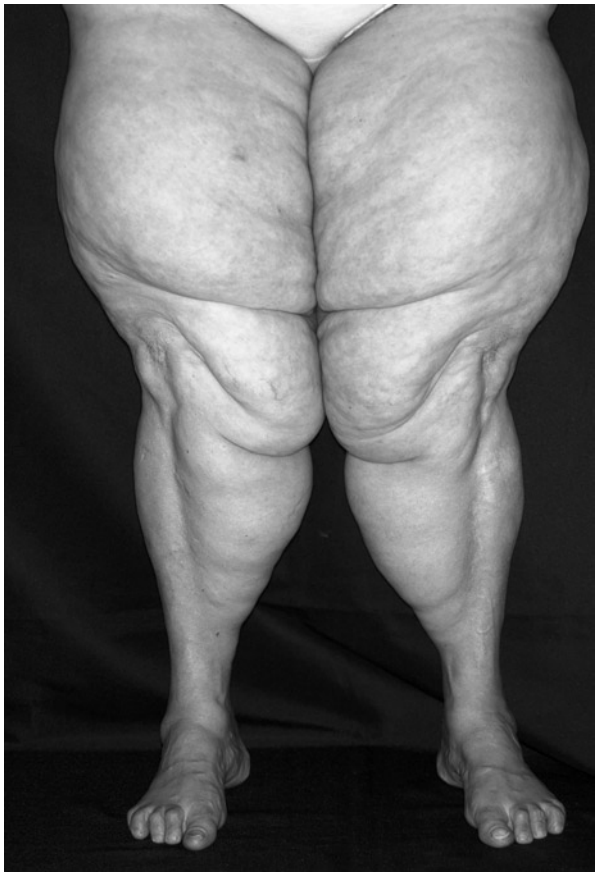

Fig. 17.3 Stage III lipedema

feet) forms. Postulated etiologies include abnormal proliferation of brown fat cells and mitochondrial mutations. It predominantly affects middle-aged men of Mediterranean origin with a history of alcohol abuse. It is usually asymptomatic; however, in advanced forms, dysphagia, diminished cervical range of motion, hoarseness and respiratory complications may appear. Glucose intolerance and increased serum insulin level are commonly found. There are signs of primary neuropathy and neurogenic muscular atrophy.

Steatopygia is characterized by protrusion and excessive adipose deposition localized solely to the buttock region.[16]

Fibro-fatty syndrome (*juxta-articular adiposis dolorosa*) shares some similarities with lipedema in having enlarged fatty mass on the thighs and the inner side of the knee joints; however, some experts consider this disorder to be an early form of Dercum's disease.[17] In half of the cases there are additional foot deformities and varicosities. Compromised lymphatic and venous circulation are believed to play a significant role in the maintenance and further progression of this disorder. It is sometimes combined with arterial hypertension.

Table 17.1 Differential diagnosis

	Gender	Family history	Onset	Location	Symmetry	Excess fat	Pain at pressure
Lipedema	Female	Possible	Puberty	Leg, arm	Yes	Yes	Yes
Lipo-hypertrophy	Female	Possible	Conva-lescent, adult	Hip	Yes	Yes	Rarely
Primary lymphedema	Female > male	Yes	From birth to third decade	Buttock, leg, arm	Uni- or bilateral	Possible	No
Phlebedema	Both	No	Adult	Leg	Uni- or bilateral	No	No
Morbus Dercum	Female	No	Menopause	Neck	Yes	Yes	Yes
Morbus Madelung	Male	No	Adult	Arms, trunk, legs	Yes	Yes	No
Obesity	Both	No	Adults	General	Yes	Yes	No

Table 17.2 Differential diagnosis

	Edema	Foot affected	Arm affected	Dietary effect	Effect of elevation	Stemmer sign
Lipedema	Yes	No	Yes	No	Minimal	No
Lipohypertrophy	No	No	Yes	No	No	No
Primary lymphedema	Yes	Yes	Possible	No	Minimal	Yes
Phlebedema	Yes	Possible	No	No	Efficient	No
Morbus Dercum	No	No	No	No	No	No
Morbus Madelung	No	No	Possible	No	No	No
Obesity	Rarely	No	Yes	Yes	No	No

Table 17.3 Differential diagnosis

	Ankle fat pad	Consistency	Pitting edema	History of cellulitis	Progression	Hereditary factor
Lipedema	Yes	Soft-to-firm	No	No	Yes	Probable
Lipo-hypertrophy	No	Soft	No	No	Possible	No
Primary lymphedema	No	Firm	Yes	Yes	Yes	Yes
Phlebedema	No	Soft-to-firm	No	No	Yes	Possible
Morbus Dercum	No	Soft-to-firm	No	No	Yes	No
Morbus Madelung	No	Soft-to-firm	No	No	Yes	No
Obesity	No	Soft	No	No	Yes	No

Laboratory Diagnosis

Waist-to-Height Ratio

Of the anthropometric measurements the waist-to-height ratio may give the most reasonable results in lipedema.[10]

Streeten Test

If cardiac, renal, and venous insufficiencies are excluded, the patient can be subjected to examination. The patient drinks 20 ml water/kg of body weight and remains in an upright position for 4 h. During this period of observation, urine is collected. The leg volume is measured prior and subsequent to the test. Normal healthy individuals excrete more than 60% of the ingested water and the leg volume does not increase by more than 350 ml/kg. Pathological results indicate the existence of increased permeability of blood capillaries.[18]

Capillary Fragility Assessment

Bruising is attributed to increased capillary fragility in lipedema.[2-4,19] Capillary fragility measurement is accomplished with a vacuum suction chamber (Parrot's angiosterrometer) exerting an adjustable suction on the skin. Determination of capillary fragility is based on the quantified petechiae. Uncomplicated simple obesity was compared with uncomplicated lipedema from the perspective of capillary fragility (unreported study). The vacuum suction method (−30 mmHg pressure for 1 min) revealed that the number of induced petechiae was significantly higher in the lipedema group, emphasizing the possible role of angiosterrometry, or other methods of capillary fragility measurement, as a potential tool for discrimination of disease.

Assessment of Aortic Distensibility and Stiffness in Lipedema

In an unreported clinical trial where women with uncomplicated lipedema were compared with healthy age- and BMI-matched individuals, lipedema was associated with notably higher aortic stiffness and lower distensibility.[20]

Pain Perception Assessment

The pinch test is the simplest method of pain detection.[2] Lipedematous pain is difficult to describe; therefore, a 30-item questionnaire was designed to characterize the most typical adjectives.[21] A four-grade scale was assigned to each item and adjectives with the highest grades referred to the most characteristic descriptions. In a comparative clinical trial the top ten items, as well as a special numerical analog scale (from 0 to 10) called the Pain Rating Scale[22] and the Wong Baker Faces scale were applied for pain assessment.[23]

Ultrasound Examination

High-resolution duplex ultrasound is a method that can distinguish lipedema from venous edema or lymphedema with a high level of sensitivity.[24,25]

Lipedematous subcutaneous tissue is definitely enlarged and has substantially higher echogenicity ("snowfall sign") without hypoechoic spaces or channels. Subcutaneous septae are thickened and have increased echogenicity. Lymphedema has thickened subcutaneous tissue with enhanced echogenicity with associated small, <1-mm hypoechoic spaces (initial dilated lymphatic vessels) and larger, longer hypoechoic spaces and channels with echo-rich margins (congested lymphatic

collectors). Beyond venous stasis and dilated veins, often varicose, no specific duplex ultrasound features are described in venous edema.

CT and MRI Examination

Computed tomography[26] and MRI[27]are typically indicated for scientific purposes or subtle cases, and show that the objective edema is minimal and that limb swelling can mostly be attributed to bilateral homogeneous enlargement of the subcutaneous compartment in the early stages of lipedema.

These examinations provide the possibility of volumetry, the evaluation of various tissue components, and the simultaneous display of blood or lymphatic vessels with high precision.[28]

Lymphoscintigraphy and Fluorescent Microlymphography

The peculiar enlargement of subcutaneous fat is presumably linked with microangiopathy and altered microcirculation, leading to increased permeability and protein-rich fluid extravasation that further enhances the amount of interstitial fluid. Therefore, in less advanced forms of lipedema, increased lymph flow may be visualized by lymphoscintigraphy. Lymph vessels must raise their transport capacity, because of augmented capillary filtration and increasing volume of interstitial fluid. In later stages the lymphatics may become exhausted.[29,30] Fluorescent microlymphography displays lymphatic microaneurysms and dilated vessels of the uppermost lymphatic network, indicating that lymph vessels are also involved.[31]

Clinical Management

The conservative approach corresponds to complex decongestive physiotherapy (CDP) consisting of manual lymph drainage (MLD) and, optionally, intermittent pneumatic compression (IPC), physical exercise, multilayered compression bandaging, and meticulous skin care.[2] The first observational study on the effect of CDP in lipedema showed that the maximally achieved reduction was nearly 10% of the original leg girth.[32] In a clinical study, MLD-based CDP was compared with MLD plus IPC-based CDP. Each treatment modality resulted in significant limb volume reduction; however, no significant difference was observed between the two regimens.[33] In other controlled trials MLD + IPC-based CDP drastically decreased capillary fragility and pain perception of lipedema patients.[19]

Various forms of surgical lipoaspiration give more reliable benefit to lipedema patients without proven damage of the lymphatics.[34]

Prognosis

Early diagnosis and treatment are mandatory for this disorder; otherwise, gradual enlargement of fatty deposition causes impaired mobility, debilitation, and further co-morbidities like arthrosis and lymphatic insufficiency. Interlobar areas may become susceptible to fungal and, especially, bacterial infections that may further progress to cellulitis or septicemia especially when lymphedema coexists. Lipedema has a remarkable psychological impact, ranging from mild upset to severe anxiety, depression or even anorexia.[2-4]

References

1. Allen EV, Hines EA. Lipedema of the legs: a syndrome characterized by fat legs and orthostatic edema. *Proc Staff Meet Mayo Clin*. 1940;15:184-187.
2. Földi E, Földi M. Das Lipödem. In: Földi M, Kubik S, eds. *Lehrbuch der Lymphologie*. 5th ed. München-Jena: Gustav Fischer; 2002:449-458.
3. Langendoen SI, Habbema L, Nijsten TE, Neumann HA. Lipoedema: from clinical presentation to therapy. A review of the literature. *Br J Dermatol*. 2009;161:980-986.
4. Todd M. Lipoedema: presentation and management. *Br J Community Nurs*. 2010;15:S10-S16.
5. Meier-Vollrath I, Schneider W, Schmeller W. Lipödem: Verbesserte Lebensqualität durch Therapiekombination. *Dtsch Ärztzeblatt*. 2005;102:1061-1067.
6. Chen S, Hsu SD, Chen TM, Wang HJ. Painful fat syndrome in a male patient. *Br J Plast Surg*. 2004;57:282-286.
7. Child AH, Gordon KD, Sharpe P, et al. Lipedema: an inherited condition. *Am J Med Genet A*. 2010;152A:970-976.
8. Szolnoky G, Kemeny L. Lipoedema: from clinical presentation to therapy: further aspects. *Br J Dermatol*. 2010;162:889.
9. Meier-Vollrath I, Schneider W, Schmeller W. Das Lipödem: neue Möglichkeiten der Therapie. *Schweiz Med Forum*. 2007;7:150-155.
10. Herpertz U. Adipositas-Diagnostik in der Lymphologie. *LymphForsch*. 2009;13:90-93.
11. Herpertz U. Das Lipödem. *Z Lymphol*. 1995;19:1-11.
12. Capeau J, Magré J, Caron-Debarle M, et al. Human lipodystrophies: genetic and acquired diseases of adipose tissue. *Endocr Dev*. 2010;19:1-20.
13. Lange U, Oelzner P, Uhlemann C. Dercum's disease (Lipomatosis dolorosa): successful therapy with pregabalin and manual lymphatic drainage and a current overview. *Rheumatol Int*. 2008;29:17-22.
14. Alameda YA, Torres L, Perez-Mitchell C, Riera A. Madelung disease: a clinical diagnosis. *Otolaryngol Head Neck Surg*. 2009;141:418-419.
15. Verna G, Kefalas N, Boriani F, Carlucci S, Choc I, Bocchiotti M. Launois-Bensaude syndrome: an unusual localization of obesity disease. *Obes Surg*. 2008;18:1313-1317.
16. Ersek RA, Bell HN. Serial and superficial suction for steatopygia (Hottentot bustle). *Aesthetic Plast Surg*. 1994;18:279-282.
17. Eisman JM, Swezey RL. Juxta-articular adiposis dolorosa. What is it? Report of 2 cases. *Ann Rheum Dis*. 1979;38:479-482.
18. Streeten DH. Idiopathic edema pathogenesis, clinical features, and treatment. *Endocrinol Metab Clin North Am*. 1995;24:531-547.
19. Szolnoky G, Nagy N, Kovács RK, et al. Complex decongestive physiotherapy decreases capillary fragility in lipedema. *Lymphology*. 2008;41:161-166.

20. Nemes A, Gavallér H, Csajbók É, Forster T, Csanády M. Obesity is associated with aortic enlargement and increased stiffness: an echocardiographic study. *Int J Cardiovasc Imaging*. 2008;24:165-171.
21. Schmeller W, Meier-Vollrath I. Schmerzen beim Lipödem: Versuch einer Annäherung. *LymphForsch*. 2008;12:7-11.
22. Hamner JB, Fleming MD. Lymphedema therapy reduces the volume of edema and pain in patients with breast cancer. *Ann Surg Oncol*. 2007;14:1904-1908.
23. Wong DL, Baker CM. Smiling faces as anchor for pain intensity scales. *Pain*. 2001;89: 295-300.
24. Marshall M, Schwahn-Schreiber C. Lymph-, Lip- und Phlebödem. Differenzialdiagnostische Abklärung mittels hochauflösender Duplexsonographie. *Gefässchirurgie*. 2008;13:204-212.
25. Naouri M, Samimi M, Atlan M, et al. High resolution cutaneous ultrasonography to differentiate lipoedema from lymphoedema. *Br J Dermatol*. 2010;163:296-301.
26. Vaughan BF. CT of swollen legs. *Clin Radiol*. 1990;41:24-30.
27. Dimakakos PB, Stefanopoulos T, Antoniades P. MRI and ultrasonographic findings in the investigation of lymphedema and lipedema. *Int Surg*. 1997;82:411-416.
28. Lohrmann C, Foeldi E, Langer M. MR imaging of the lymphatic system in patients with lipedema and lipo-lymphedema. *Microvasc Res*. 2009;77:335-339.
29. Brauer WJ. Altersbezogene Funktionslymphszintigraphie beim Lipödem und Lipolymphödem. *LymphForsch*. 2000;4:74-77.
30. Harwood CA, Bull RH, Evans J, Mortimer PS. Lymphatic and venous function in lipedema. *Br J Dermatol*. 1996;134:1-6.
31. Amann-Vesti BR, Franzeck UK, Bollinger A. Microlymphatic aneurysms in patients with lipedema. *Lymphology*. 2000;134:170-175.
32. Deri G, Weissleder H. Vergleichende prä- und posttherapeutische Volumenmessungen in Beinsegmenten beim Lipödem. *LymphForsch*. 1997;1:35-37.
33. Szolnoky G, Borsos B, Bársony K, Balogh M, Kemény L. Complete decongestive physiotherapy of lipedema with or without pneumatic compression: a pilot study. *Lymphology*. 2008;41:50-52.
34. Schmeller W, Meier-Vollrath I. Tumescent liposuction: a new and successful therapy for lipedema. *J Cutan Med Surg*. 2006;10:7-10.