

Original Article

# Lymphoscintigraphic findings in patients with lipedema<sup>☆</sup>

I. Forner-Cordero <sup>a,\*</sup>, P. Oliván-Sasot <sup>b</sup>, C. Ruiz-Llorca <sup>b</sup>, J. Muñoz-Langa <sup>c</sup>



<sup>a</sup> Unidad de Linfedema, Hospital Universitari i Politècnic La Fe, Universidad de Valencia, Valencia, Spain

<sup>b</sup> Servicio de Medicina Nuclear, Hospital Universitari i Politècnic La Fe, Valencia, Spain

<sup>c</sup> Servicio de Oncología Médica, Hospital Universitari i Politècnic La Fe, Valencia, Spain

## ARTICLE INFO

### Article history:

Received 22 April 2018

Accepted 26 June 2018

Available online 29 October 2018

### Keywords:

Lipedema

Lymphoscintigraphy

Lymphedema

Edema

## ABSTRACT

**Introduction:** Lipoedema is a syndrome that is characterized by edema, an accumulation of fat, pain and haematomas in the lower limbs that principally affects women. Diagnosis is currently based on clinical criteria, since there is no accurate diagnostic imaging for the condition. The aim of our study was to describe the lymphoscintigraphic findings in patients with lipoedema.

**Material and method:** A prospective cohort study of women with clinical criteria of lipoedema who underwent lymphoscintigraphy. Two independent nuclear physicians described and classified the lymphoscintigraphy findings in different grades of severity, according to the migration and distribution of the radiopharmaceutical.

Eighty-three patients were included with a median age of 49.7 years (range: 18–80) and a mean body mass index (BMI) of 29.9 kg/m<sup>2</sup> (95% CI: 28.4–31.3).

**Results:** Lymphoscintigraphy showed alterations in 47% of the patients, most were low (35.9%) or low-moderate grade (48.7%). None of the patients were severely affected (no migration of the radio-pharmaceutical).

The degree of lymphoscintigraphic involvement showed no relation to age ( $p=0.674$ ), Stemmer's sign ( $p=0.506$ ), or BMI ( $p=0.832$ ). We found lymphoscintigraphy findings in all the clinical stages of lipoedema, with no significant differences between the grade of lymphoscintigraphic involvement and the clinical stage of lipoedema ( $p=0.142$ ).

**Conclusion:** Although lymphoscintigraphy has been used to differentiate lipoedema from lymphoedema, we found frequent alterations in the patients with lipoedema, therefore the presence of findings does not rule out a diagnosis of lipoedema.

© 2018 Sociedad Española de Medicina Nuclear e Imagen Molecular. Published by Elsevier España, S.L.U. All rights reserved.

## Hallazgos linfogammagráficos en pacientes con lipedema

## RESUMEN

### Palabras clave:

Lipedema

Linfogammagrafía

Linfedema

Edema

**Introducción:** El lipedema es un síndrome caracterizado por edema, acúmulo de grasa, dolor y hematomas en miembros inferiores que afecta principalmente a mujeres. Su diagnóstico actual se basa en criterios clínicos, dado que no tiene un diagnóstico de imagen de certeza. El objetivo de nuestro estudio fue describir los hallazgos linfogammagráficos observados en pacientes con lipedema.

**Material y método:** Estudio de cohortes prospectivo de mujeres con criterios clínicos de lipedema a las que se realizó una linfogammagrafía. Dos médicos nucleares independientes describieron y clasificaron los hallazgos linfogammagráficos en diferentes grados de gravedad, en función de la migración y de la distribución del radiofármaco.

Fueron incluidas 83 pacientes con una mediana de edad de 49,7 años (rango: 18–80) y un índice medio de masa corporal (IMC) de 29,9 kg/m<sup>2</sup> (IC 95%: 28,4–31,3).

**Resultados:** En el 47% de las pacientes se observó alguna alteración en la linfogammagrafía, siendo en la mayoría de bajo grado (35,9%) o de grado bajo-moderado (48,7%). Ninguna presentó afectación severa (no migración del radiofármaco).

El grado de afectación linfogammagráfica no presentó relación con la edad ( $p=0,674$ ), ni con el signo de Stemmer ( $p=0,506$ ), ni con el IMC ( $p=0,832$ ). Encontramos hallazgos linfogammagráficos en todos los estadios clínicos de lipedema, sin diferencias significativas entre el grado de afectación linfogammagráfico y el estadio clínico del lipedema ( $p=0,142$ ).

<sup>☆</sup> Please cite this article as: Forner-Cordero I, Oliván-Sasot P, Ruiz-Llorca C, Muñoz-Langa J. Hallazgos linfogammagráficos en pacientes con lipedema. Rev Esp Med Nucl Imagen Mol. 2018;37:341–348.

\* Corresponding author.

E-mail addresses: [ifornercordero@gmail.com](mailto:ifornercordero@gmail.com), [forner\\_isa@gva.es](mailto:forner_isa@gva.es) (I. Forner-Cordero).

**Conclusión:** Aunque la linfogammagrafía se ha empleado para diferenciar lipedema de linfedema, encontramos alteraciones frecuentes en las pacientes con lipedema, por lo que la presencia de hallazgos no descarta el diagnóstico de lipedema.

© 2018 Sociedad Española de

Medicina Nuclear e Imagen Molecular. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

## Introduction

Lipedema is a syndrome which was first described by Allen and Hines in 1940. It is characterized by edema, fat deposits, pain and frequent bruising of the lower limbs. It mainly affects women and is usually symmetrical.<sup>1</sup>

Although it has been estimated that lipedema affects from 0.06 to 10% of the female population,<sup>2</sup> this disease is underdiagnosed<sup>3,4</sup> and has an important impact on patient quality of life. Lipedema affects almost 19% of the patients attended in the Lymphedema Unit of our hospital.<sup>4</sup> Five years ago the European Society of Lymphology requested the inclusion of lipedema on the ICD11 list of the World Health Organization, and finally, in May 2018 it was officially included on this list under the section “EFO2.2LIPEDEMA. Noninflammatory alterations of subcutaneous fat”.

Lipedema is a chronic disease which appears during puberty, although it has also been described after pregnancy or in menopause.<sup>1</sup> Patients present an abnormal, symmetric increase in adipose tissue in the hips, thighs and legs which may also affect the upper limbs in one third of the patients.<sup>5</sup> In contrast to lymphedema, it does not usually affect either the feet or the lower part of the ankle, being abruptly detained at the ankle joint (Fig. 1); this is called the “cuff sign” or the “bracelet effect” or the “handcuffs” in the case of the arms.<sup>6</sup>

Edema of the lower limbs usually worsens in the evening and at night in relation to orthostatism and heat. Patients also complain of increased sensitivity to pain and a tendency to develop subcutaneous bruises with only minimum trauma. Other symptoms which may appear include: alteration of the plantar arch, skin coldness and spontaneous pain. On progression of the lipedema and an important increase in volume, difficulty in walking can incapacitate the patient, and it is often associated with arthrosis of the hips and knees.

The etiopathogenesis of lipedema is unknown although multiple factors influence the clinical manifestations.<sup>7</sup> Genetic studies suggest autosomal dominant inheritance which rarely affects males.<sup>8</sup> Pathological studies have shown an increase in fat which may be due to adipocyte hyperplasia and hypertrophy and cell death by hypoxia.<sup>9</sup> An increase in capillary filtrate has also been observed which overloads a morphologically normal lymphatic system and increases capillary fragility which causes the hematomas.<sup>2</sup>

In 1951, Wold et al.<sup>10</sup> published the first diagnostic criteria of lipedema which were later modified by Herbst<sup>11</sup> (Table 1).

There is currently no pathognomonic test for lipedema, and the differential diagnosis with lymphedema has traditionally been made by lymphoscintigraphy since theoretically lipedema is not associated with dysfunction of the lymphatic system in the early stages. Taking all of this into account, the aim of the present study was to describe the lymphoscintigraphic findings in a cohort of patients with lipedema.

## Material and methods

### Study design

This was a prospective cohort study of patients clinically diagnosed with lipedema who underwent lymphoscintigraphy to

**Table 1**  
Diagnostic criteria of lipedema.

Almost exclusively affects women
Bilateral symmetric involvement with sparing of the feet
Minimum pitting edema
Negative Stemmer's sign <sup>a</sup>
Pain on application of pressure
Hematomas with minimum trauma
Increase in the volume of the lower limbs despite weight loss or elevation of the limbs
Arms affected in 30% of the cases <sup>b</sup>
Skin hypothermia <sup>b</sup>
Worsening of the edema when standing or in the summer <sup>b</sup>
Not modified with calorie restriction <sup>b</sup>
Telangiectasias <sup>b</sup>

<sup>a</sup> The Stemmer's sign is positive when it is not possible to pinch the skin of the middle finger.

<sup>b</sup> Added by Herbst.<sup>11</sup>

describe the prevalence and the type of lymphoscintigraphic alterations in these patients.

The inclusion criteria were: women over 18 years of age presenting a bilateral increase in lower limb volume associated with at least three of the following symptoms which are characteristic of lipedema: spontaneous pain in the lower limbs, bruising with minimum trauma, disproportion of fat distribution between the upper and lower body, sparing the feet and with a negative Stemmer's sign (this sign is positive when the skin of the middle finger or second toe cannot be pinched<sup>1</sup>).

Patients with the following criteria were excluded from the study: patients with systemic, hepatic, renal, or tumoral diseases or those who were unable to provide consent to participate in the study. Informed consent was obtained from all the patients included, and the study was approved by the Ethical Committee of Biomedical Investigation of our hospital (registration number 2014/0099).

At present, lipedema is classified according to the localization of the fat deposits and the severity of the clinical alterations.

Based on the localization of the adiposity there are 5 types of presentation of lipedema<sup>11–16</sup>:

- Type I: Increase of adipose tissue in the buttocks, hips and thighs.
- Type II: Lipedema extends to the knees, with formation of folds of fat around the inner side of the knees.
- Type III: Lipedema extends from the buttocks to the ankles.
- Type IV: The arms are affected.
- Type V: The lower part of the legs is involved.

Following examination and palpation, lipedema can be classified into 4 clinical stages of severity<sup>11–16</sup>:

- Stage 1. The skin surface is normal and the subcutaneous fatty tissue is soft in consistency, although multiple nodules can be palpated.
- Stage 2. The skin surface is irregular or pitted and with the possible appearance of the orange skin phenomenon on applying pressure to the skin. The nodules may vary in size from that of a walnut up to that of an apple.



**Fig. 1.** Stage 3 lipedema with a normal lymphoscintigraphy.

- Stage 3. This stage is characterized by lobular deformation of the skin surface due to the increase of adipose tissue.
- Stage 4. Lipolymphedema.

#### Description of the lymphoscintigraphy

Lymphoscintigraphy is begun with the subcutaneous injection of 22.2 MBq of  $^{99m}\text{Tc}$  albumin nanocolloid in a small volume of saline solution (<0.2 ml).<sup>17</sup> A total of 4 injections are made in the first and third interdigital spaces of each foot. Both lower limbs are always studied to thereby determine unsuspected alterations in some cases, and if one of the limbs shows normal lymph drainage this can be used for comparison.

Following the injection, the patients are asked to do some mild exercise (i.e. walking for 10 min) in order to activate the lymph function and favor maximum drainage.<sup>17</sup> Afterwards, at 15 and 180 min post-injection, a whole body scan is performed.

Two independent nuclear medicine physicians reported the lymphoscintigraphic findings and classified these into different grades according to a visual scale developed by these physicians for maximum reproducibility (Figs. 1–4):

- 0: Normal.
- 1: Low grade. Delay in radiotracer migration or slight asymmetry in its distribution.
- 2: Low-moderate grade. Migration of the radiotracer and lymph node filling of slightly altered characteristics suggestive of mild lymphatic hypoplasia.
- 3: Moderate grade. Migration of the radiotracer and lymph node filling of moderately altered characteristics suggestive of moderate lymphatic hypoplasia.

- 4: Moderate-severe grade. Migration of the radiotracer and lymph node filling of markedly altered characteristics suggestive of severe lymphatic hypoplasia.
- 5: Severe grade. No migration of the radiotracer, with no lymphatic filling during the study, suggesting the presence of lymphatic aplasia.

An extra point of classification was added if there was diffuse dermal reflux or retention of the radiotracer at the level of the popliteal fossa.

#### Statistical analysis

The results of the descriptive analysis of the data are presented as central tendency and dispersion (mean, median, 95% confidence interval [CI] and range) for continuous variables and absolute and relative frequencies were calculated for categorical variables.

In the inferential statistical analysis of the data, the Levene variance homogeneity test and the Kolmogorov-Smirnov test were used to assess the degree of normality of the continuous variables, using tests of parametric hypotheses whenever possible. In all cases, the bilateral hypothesis tests were performed and applied with a level of significance of 5% ( $p \leq 0.05$ ) and a power of 80%.

The comparison of non ordinal categorical variables was done using contingency tables with the Chi-square test, and the Fisher or Yates test was used for continuity correction when appropriate.

Analysis of variance (ANOVA test) was used to study the relationship between categorical and non-dependent quantitative variables.

The statistical analyses were performed with the SPSS Statistics version 22 (IBM Corporation; Armonk, NY, USA).



**Fig. 2.** Stage 1 lipedema with low-moderate grade lymphoscintigraphic alterations.

### Characteristics of the study population

From September 2012 to December 2016 110 patients with lipedema were recruited. Of these, 83 fulfilled the inclusion criteria and had undergone lymphoscintigraphy and were included in the study.

The median age of the patients was 49.7 years (range: 18–80). Lipedema symptoms had begun at a mean age of 20.4 years (standard deviation [SD]: 12.65), although the clinical diagnosis was made at a mean age of 46.5 years (SD: 15.30), with a delay of 26.1 years since the onset of the clinical manifestations.

The mean body mass index (BMI) was 29.9 kg/m<sup>2</sup> (95% CI: 28.4–31.3).

Type III was the most frequent type of lipedema (74.7% of the patients), being localized from the buttocks to the ankles, with sparing of the feet.

The most frequent stage of clinical severity was stage 1 (40.2%). Most of the patients reported a family history of lipedema (89%) (Table 2).

## Results

### Clinical characteristics

The most frequent clinical manifestations of lipedema presented were bilateral and symmetric involvement (100%), disproportion between the upper and lower body (92.8%), pain (92.8%), sparing of the feet (89.2%) and spontaneous bruising or the development of hematomas with minimum trauma (88%) (Table 3).

**Table 2**  
Demographic and clinical characteristics.

Patients	(n=83)
Age (years) (median; range)	49.7 (18–80)
Body mass index (kg/m <sup>2</sup> ) (mean; 95%CI)	29.9 (28.4–31.3)
Age at onset (years) (median; range)	15.0 (4–60)
Delay until diagnosis (years) (mean; SD)	26.1 (15.4)
<i>Clinical stage of lipedema</i>	
1	33 (39.8%)
2	21 (25.3%)
3	23 (27.7%)
4	6 (7.2%)
<i>Type of lipedema</i>	
I: buttocks	0%
II: buttocks and thighs to the knees	11 (13.3%)
III: from hips to ankles	62 (74.7%)
IV: arms and legs	9 (10.8%)
V: lower part of the legs	1 (1.2%)
<i>Onset related to:</i>	
Puberty	43 (51.8%)
Oral contraceptives	1 (1.2%)
Pregnancy	15 (18.1%)
Menopause	6 (7.2%)
Others	18 (21.7%)
<i>Family history of lipedema.</i>	
No. of first degree relatives affected (mean; 95%CI)	74 (89.2%)
No. of second degree relatives affected (mean; 95%CI)	1.1 (0.9–1.3)
	1.4 (1.1–1.8)

CI: confidence interval; SD: standard deviation.

### Lymphoscintigraphic findings

Forty-seven percent of the patients presented some alteration in the lymphoscintigraphy. In most cases these findings were mild



**Fig. 3.** Stage 2 lipedema with low–moderate lymphoscintigraphic alterations.

**Table 3**  
Description of the characteristic signs and symptoms of lipedema.

Patients	(n=83)
Bilateral and symmetric involvement	83 (100%)
Disproportion between the upper and lower body	77 (92.8%)
Pain	77 (92.8%)
Feet spared	74 (89.2%)
Hematomas	73 (88%)
Vascular spiders	71 (86.6%)
Stemmer's sign	67 (80.7%)
Skin coldness	33 (41.3%)
Pitting	14 (16.9%)
Fibrosis	8 (9.6%)

**Table 4**  
Lymphoscintigraphic alterations.

Patients	(n=83)
Patients with some grade of involvement	39 (47%)
<i>Grade of alteration:</i>	
1 – Low	14 (35.9%)
2 – Low-moderate	19 (48.7%)
3 – Moderate	6 (15.4%)
4 – Moderate-severe	0%
5 – Severe	0%

(84.6%): of low grade with slight asymmetry in lymphatic function of the lower limbs or delay in radiotracer uptake or low-moderate grade with slight hypoplasia. No patient showed severe involvement in the lymphoscintigraphic study (Table 4).

The grade of lymphoscintigraphic involvement was not related to the age of the patient ( $p=0.674$ ) or with the presence or absence of Stemmer's sign ( $p=0.506$ ). Neither were these

lymphoscintigraphic alterations associated with the BMI ( $p=0.832$ ). The chronicity of lipedema was not related to the presence or absence of lymphoscintigraphic findings ( $p=0.324$ ) or with the severity of these findings ( $p=0.274$ ).

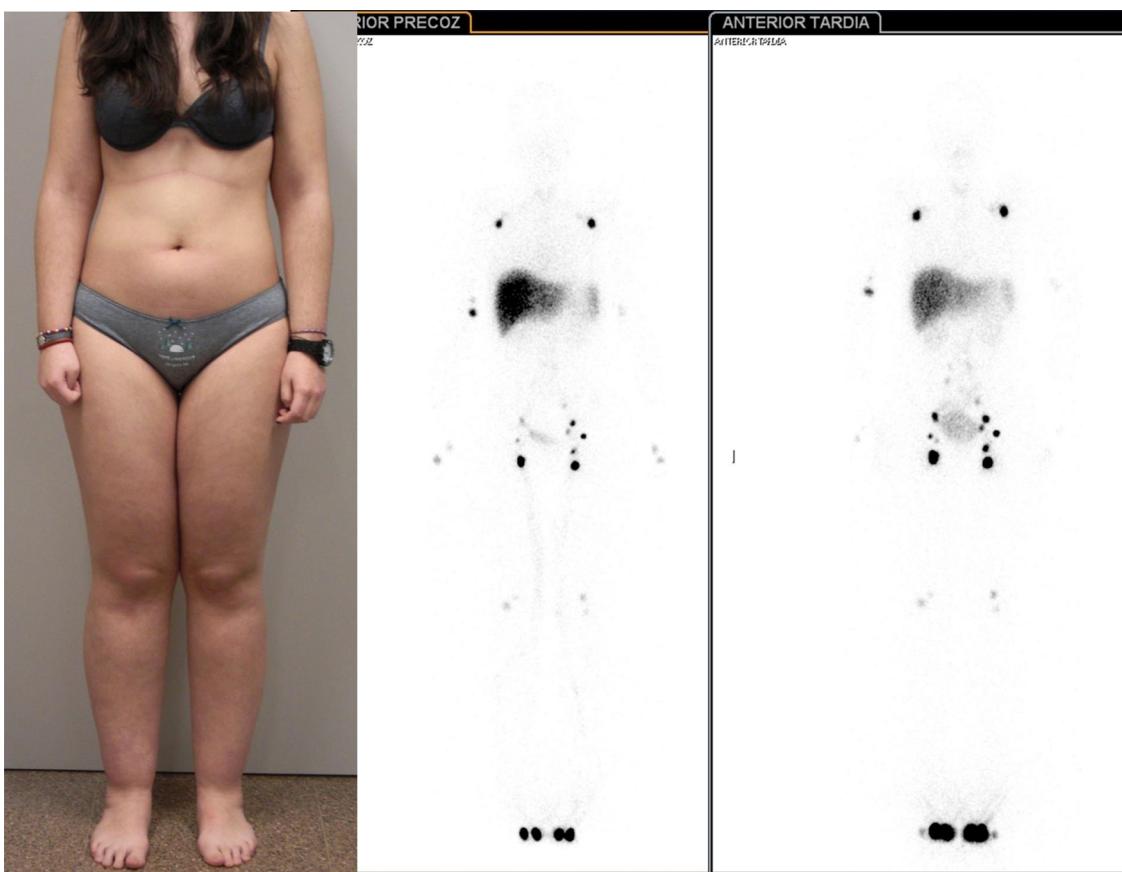
Lymphoscintigraphic alterations were observed in all the stages of lipedema even in clinical stage 1 (Fig. 5), with no significant differences between the clinical stage and the grade of involvement in the lymphoscintigraphy ( $p=0.142$ ) (Figs. 1–4).

Neither were there significant differences between the type of lipedema and the presence of lymphoscintigraphic findings ( $p=0.505$ ).

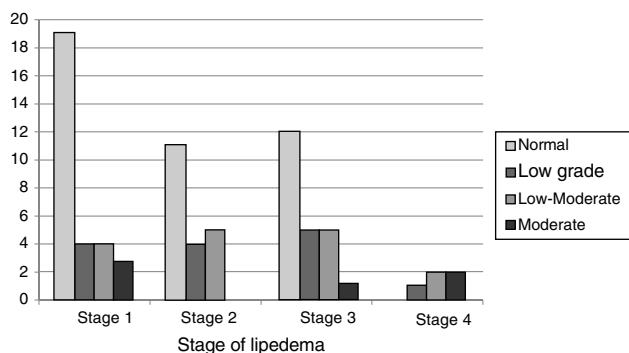
## Discussion

Since differentiation between lipedema and lymphedema and lipedema and obesity is not always clear, the lack of a test of diagnostic certainty makes the diagnosis, and moreover, the investigation of lipedema difficult. Therefore, as described in several clinical guidelines, there is a clear need for a reliable test to accurately diagnose lipedema.<sup>13–16</sup>

Lymphoscintigraphy is a diagnostic imaging technique which uses albumin nanocolloids labeled with  $^{99m}\text{Tc}$  to study the functioning of the lymphatic system at any localization and has therefore been traditionally used to differentiate lipedema from lymphedema. To achieve this objective the characteristics of the radiotracer used are very well defined, the most important being the size of the particle, the speed of migration and the capacity of uptake at a lymph node level.<sup>18</sup> We use  $^{99m}\text{Tc}$  albumin nanocolloids in our hospital. This radiotracer is the most frequently used in Europe to perform lymphoscintigraphy, although there are other radiotracers with similar characteristics.<sup>18</sup>



**Fig. 4.** Moderate findings in an 18-year-old female with stage 2 lipedema.



**Fig. 5.** Grade of lymphoscintigraphic involvement in the different stages of lipedema.

It is of note that there is currently no wide consensus as to a specific work protocol (probably because of the low demand for this technique and the small number of studies made in Nuclear Medicine Departments), and therefore, there is some controversy as to the route of radiotracer administration, the volume and activity to be injected and the optimum time for image acquisition. With regard to the route of administration, some authors prefer intradermal injection while others such as Szuba and Rockson,<sup>19</sup> prefer subcutaneous injection. This latter route is probably better than intradermal injection for analyzing the epifascial and subfascial lymphatic compartments.<sup>20</sup> Considering the volume to be administered, the study by Bourgeois<sup>21</sup> concluded that, as in our study, a low volume is preferable in lymphoscintigraphy (0.2 ml) with an elevated concentration of the radiotracer.

The interpretation of lymphoscintigraphic images involves classical findings described by most authors and other less frequent results. In our case we classified the findings based on the presence or not of radiotracer migration from the injection points. This migration showed either diffuse activity as an ascending lymphatic path, the presence of collateral pathways or with focal filling (considered as lymph nodal) at the femoral, inguinal and pelvic level within the superficial lymphatic drainage and at a popliteal level as part of deep drainage.<sup>19,22</sup>

Although some authors such as Infante et al.<sup>20</sup> do not consider the appearance of deep lymph nodes or the development of collateral paths as key in the diagnosis of lipedema, other authors such as Karaçavuş et al.<sup>22</sup> do take these into account since these findings are considered to be the consequence of deterioration of the superficial lymphatic system, and the presence of deep lymph nodes has been related to the length of lymphedema evolution. We decided to add an extra point to our classification of the grade of scintigraphic alteration in the studies showing the presence of diffuse dermal activity or the appearance of deep lymph nodes in order to demonstrate the greater alteration of lymphatic function which seems to occur in these cases.

Although echo-doppler, axial computerized tomography and magnetic resonance studies provide data for the diagnosis of lower limb edema,<sup>23</sup> lymphoscintigraphy has traditionally been considered as an essential test for the diagnosis of diseases of the lymphatic pathways.<sup>24,25</sup> In a recent study including a large number of patients, lymphoscintigraphy presented a sensitivity of 96% and a specificity of 100% in the diagnosis of lymphatic disease.<sup>26</sup> One of the important advances in the last years is the visualization of the lymphatic system using a lympho-fluoroscopy with indocyanine green which provides an immediate, noninvasive, *in vivo* image able

to visualize contractile lymphatic propulsion.<sup>27</sup> Nonetheless, different studies are ongoing to compare lymphoscintigraphy, which still continues to be considered the gold standard, and the new diagnostic techniques in order to determine the most adequate test for the study of the lymphatic system.<sup>27</sup>

Lymphoscintigraphic alterations are typically associated with the diagnosis of lymphedema and are used to differentiate this disease from lipedema.<sup>28</sup> However, we observed that these alterations are present in up to 47% of the patients with lipedema.

Another study showed the presence of insufficiency of the lymphatic system in patients with lipedema without morphological alterations in the lymphoscintigraphy study, which may help to differentiate lipedema from lymphedema. However, the sample was small, and therefore, the lymphoscintigraphic findings may not have been representative.<sup>29</sup>

In a study of 12 women with lipedema, Bilancini et al.<sup>30</sup> observed marked slowness of the drainage of the lymphatic system in the lymphoscintigraphy compared with healthy subjects. These findings were similar to those described in patients with lymphedema, and it was also found that these alterations were asymmetric in contrast with the characteristically symmetric involvement of lipedema (Fig. 2).

Our results also support the idea that the absence of scintigraphic alterations is not pathognomonic of lipedema since 47% of the patients presented some lymphoscintigraphic alteration. This is shown in the cases of Figs. 2–4, in which patients with lipedema demonstrate lymphoscintigraphic findings of different severity.

In the clinical staging according to the severity of lipedema, stage 4 or lipolymphedema suggests the presence of secondary involvement of the lymphatic system and that lipedema progresses over time. However, greater involvement was not observed in the lymphoscintigraphy or with a higher lipedema stage or older age of the patient, with scintigraphic alterations also sometimes appearing at early ages (Fig. 4). It remains to be determined whether patients with lipedema really clinically progress over time or the worsening of their condition depends on other factors. Indeed, Földi and Földi<sup>1</sup> suggested that up to 17% of the patients treated for lymphedema also have lipedema.

It could be considered that cases of lipedema with a positive Stemmer's sign, which is the diagnostic hallmark of lymphedema, have a false diagnosis of lipedema. However, in our sample the presence or not of a positive Stemmer's sign was not related to lymphatic dysfunction in the lymphoscintigraphy, indicating that there is no relationship between a positive Stemmer's sign, scintigraphic alterations and the diagnosis of lymphedema. It can, however, be stated that patients with lipedema may present a positive Stemmer's sign and/or lymphoscintigraphic alterations in any of the stages of the disease.

## Limitations

One of the limitations of the present study is that because of the lack of a test of diagnostic certainty of lipedema we may have included patients with lymphedema instead of lipedema and this would justify the lymphoscintigraphic findings. This limitation has been corrected with the inclusion criteria since the clinical diagnosis of lipedema requires fulfillment of several criteria. Nonetheless, at present it remains unknown whether different entities with different physiopathological mechanisms are included under this term of lipedema, thereby justifying the different evolution of the patients. Notwithstanding, the inclusion criteria of the present study were aimed at ruling out any patient suspected of having lymphedema in order to obtain a sample of cases of true lipedema.

## Conclusion

In conclusion, although lymphoscintigraphy has classically been used to differentiate lipedema from lymphedema, we found alterations in lymphatic function in patients with lipedema. This indicates that the presence of alterations in the lymphoscintigraphy does not rule out the diagnosis of lipedema, and the absence of these findings supports this diagnosis. The patients could present both syndromes or there could be an underlying primary or secondary lymphatic dysfunction.

The patients included in this study are being followed over time to answer these questions. The development of possible clinical algorithms to help the differential diagnosis between lipedema and lymphedema is needed until a pathognomonic diagnostic test is available.

## Conflict of interests

None.

## References

- Földi E, Földi M. Lipedema. In: Földi M, Földi E, editors. Földi's textbook of lymphology. Munich, Germany: Elsevier GmbH; 2006. p. 417–27.
- Fife CE, Maus EA, Carter MJ. Lipedema: a frequently misdiagnosed and misunderstood fatty deposition syndrome. *Adv Skin Wound Care*. 2010;23:81–92.
- Warren Peled A, Kappos EA. Lipedema: diagnostic and management challenges. *Int J Womens Health*. 2016;8:389–95.
- Forner-Cordero I, Szolnoky G, Forner-Cordero A, Kemény L. Lipedema: an overview of its clinical manifestations, diagnosis and treatment of the disproportional fatty deposition syndrome – systematic review. *Clin Obes*. 2012;2:86–95.
- Herpertz U. Krankheitsspektrum des lipedems an einer lymphologischen fachklinik – erscheinungsformen, mischbilder und behandlungsmöglichkeiten. *Vasomed*. 1997;5:301–7.
- Langendoen SI, Habbema L, Nijsten TE, Neumann HA. Lipoedema: from clinical presentation to therapy. A review of the literature. *Br J Dermatol*. 2009;161:980–6.
- Szél EL, Kemény L, Groma G, Szolnoky G. Pathophysiological dilemmas of lipedema. *Med Hypotheses*. 2014;83:599–606.
- Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S, et al. Lipedema: an inherited condition. *Am J Med Genet A*. 2010;152A:970–6.
- Suga H, Araki J, Aoi N, Kato H, Higashino T, Yoshimura K. Adipose tissue remodeling in lipedema: adipocyte death and concurrent regeneration. *J Cutan Pathol*. 2009;36:1293–8.
- 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.
- Herbst KL. Rare adipose disorders (RADs) masquerading as obesity. *Acta Pharmacol Sin*. 2012;33:155–72.
- Schmeller W, Meier-Vollrath I. Das lipodem: neue möglichkeiten der therapie. *Schweiz Med Forum*. 2007;7:150–5.
- Halk AB, Damstra RJ. First Dutch guidelines on lipedema using the international classification of functioning, disability and health. *Phlebology*. 2017;32:152–9.
- Lontok E, Briggs L, Donlan M, Kim Y, Mosley E, Riley EAU, et al. Lipedema. A giving smarter guide. Milken Institute Center for Strategic Philanthropy; 2017.
- Wounds UK. Best practice guidelines: the management of lipoedema. London: Wounds UK; 2017.
- Dayan E, Kim JN, Smith ML, editors. Lipedema – the disease they call FAT: an overview for clinicians. Boston, MA: Lipedema Simplified Publications, The Friedman Center for Lymphedema Research and Treatment at The Center for Advanced Medicine at Northwell Health in collaboration with Lymphatic Education & Research Network (LE&RN); 2017.
- Bourgeois P. Critical analysis of the literature on the lymphoscintigraphic investigations of the limb edemas. *Eur J Lymphology Relat Probl*. 1996;6:1–9.
- Giammarile F, Alazraki N, Aarsvold JN, Audisio RA, Glass E, Grant SF, et al. The EANM and SNMMI practice guideline for lymphoscintigraphy and sentinel node localization in breast cancer. *Eur J Nucl Med Mol Imaging*. 2013;40:1932–47.
- Szuba A, Rockson SG. Lymphedema: classification, diagnosis and therapy. *Vasc Med*. 1998;3:145–56.
- Infante JR, García I, Laguna P, Durán C, Rayo JL, Serrano J, et al. Linfogrammagrafía en el diagnóstico diferencial del edema. Rendimiento diagnóstico de diferentes patrones gammográficos. *Rev Esp Med Nucl Imagen Mol*. 2012;31:237–42.
- Bourgeois P. Scintigraphic investigations of the lymphatic system: the influence of injected volume and quantity of labeled colloidal tracer. *J Nucl Med*. 2007;48:693–5.
- Karaçavuş S, Yılmaz YK, Ekim H. Clinical significance of lymphoscintigraphy findings in the evaluation of lower extremity lymphedema. *Mol Imaging Radionucl Ther*. 2015;24:80–4.
- Cuello-Villaverde E, Forner-Cordero I, Forner-Cordero A. Linfedema: métodos de medición y criterios diagnósticos. *Rehabilitacion*. 2010;44 Suppl. 1:21–8.

24. Gloviczki P, Calcagno D, Schirger A, Pairolo PC, Cherry KJ, Hallet JW, et al. Noninvasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphic examinations. *J Vasc Surg.* 1989;9:683–9.
25. Ter SE, Alavi A, Kim CK, Merli G. Lymphoscintigraphy. A reliable test for the diagnosis of lymphedema. *Clin Nucl Med.* 1993;18:646–54.
26. Hassanein AH, Maclellan RA, Grant FD, Greene AK. Diagnostic accuracy of lymphoscintigraphy for lymphedema and analysis of false-negative tests. *Plast Reconstr Surg Glob Open.* 2017;5:e1396.
27. O'Donnell TF Jr, Rasmussen JC, Sevick-Muraca EM. New diagnostic modalities in the evaluation of lymphedema. *J Vasc Surg Venous Lymphat Disord.* 2017;5:261–73.
28. Szuba A, Shin WS, Strauss HW, Rockson S. The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nucl Med.* 2003;44:43–57.
29. Boursier V, Pecking A, Vignes S. Analyse comparative de la lymphoscintigraphie au cours des lipœdèmes et des lymphoœdèmes primitifs des membres inférieurs. *J Mal Vasc.* 2004;29:257–61.
30. Bilancini S, Lucchi M, Tucci S, Eleuteri P. Functional lymphatic alterations in patients suffering from lipedema. *Angiology.* 1995;46:333–9.