Metabolic and immunological phenotype of rare lipomatoses: Dercum's disease and Roch-Leri mesosomatic lipomatosis

LEMAITRE Madleen (✉ madleen.lemaitre@chru-lille.fr)
 CHRU LILLE   https://orcid.org/0000-0002-3203-717X

Benjamin CHEVALIER
 CHRU Lille Pôle Spécialités médicochirurgicales: Centre Hospitalier Regional Universitaire de Lille Pole Specialites medicochirurgicales

Arnaud JANNIN
 CHRU Lille Pôle Spécialités médicochirurgicales: Centre Hospitalier Regional Universitaire de Lille Pole Specialites medicochirurgicales

Kristell LE MAPIHAN
 CHRU Lille Pôle Spécialités médicochirurgicales: Centre Hospitalier Regional Universitaire de Lille Pole Specialites medicochirurgicales

Samuel BOURY
 CHRU de Lille Radiologie et Imagerie Médicale: Centre Hospitalier Regional Universitaire de Lille Radiologie et Imagerie Medicale

Georges LION
 CHRU de Lille Radiologie et Imagerie Médicale: Centre Hospitalier Regional Universitaire de Lille Radiologie et Imagerie Medicale

Myriam LABALETTE
 CHRU de Lille CBP: Centre Hospitalier Regional Universitaire de Lille Pole de Biologie Pathologie Genetique

Marie-christine VANTYGHEM
 CHRU Lille Pôle Spécialités médicochirurgicales: Centre Hospitalier Regional Universitaire de Lille Pole Specialites medicochirurgicales

---

Research Article

Abstract

Context

Dercum's disease (DD) and Roch-Leri mesosomatic lipomatosis (LMS) are rare and poorly characteri -zed diseases. The clinical presentation combines multiple lipomas, painful in DD in contrast with LMS, without lipoatrophy.

Objective

To identify any specific metabolic and immune phenotype of DD and LMS with the aim to improve their treatment.

Design & Patients

This monocentric retrospective study included 38 patients: 9 DD, 11 LMS and 18 healthy controls. Metabolic and immunohematological characteristics of each group were compared.

Results

The median age of the patients was similar in the 3 groups (31 years). The number of women, and of basophils, and CD3$^+$, CD4$^+$ and CD8$^+$ T lymphocytes was significantly higher in the DD *versus* the LMS group, without any difference of the metabolic parameters. Weight, BMI, blood pressure, gamma-GT, leptin, fasting insulin and C-peptide levels, fat mass percentage, and intra/total abdominal fat ratio were significantly higher in each lipomatosis group compared with the control group. Compared with the control group, the DD group had significantly higher fasting blood glucose, LDL-cholesterol, platelets, leukocytes, basophils, and a lower NK cell count, whereas the LMS group had a significantly lower rate of CD3, CD4, and CD8 lymphocytes.

Conclusion

DD and LMS show a common background of obesity and metabolic phenotype, but a distinct immunohematological profile characterized by a higher number of platelets, leukocytes and basophils in DD patients, an inflammatory profile that could contribute to pain. T lymphocyte depletion was present in LMS. These findings could offer specific therapeutic opportunities, especially for painful DD.

NCT0178428

Introduction

Lipodystrophy syndromes are rare diseases characterized by a limited capacity of subcutaneous adipose tissue to store triglycerides, which results in metabolic abnormalities such as insulin resistance, hypertriglyceridemia, fatty liver disease and polycystic ovary syndrome. Apart from these syndromes that

are usually associated with partial or generalized lipoatrophy, lipomatosis is defined by the presence of multiple lipomas on the body, without lipoatrophy (1, 2, 3).

Different entities accompanied by multiple lipomas have been described, including:

- Syndromic lipomatosis, such as those encountered in type 1 Multiple Endocrine Neoplasia or certain genetically determined multiple lipomatosis (4);

- Multiple symmetric lipomatosis, most often linked to alcohol (Madelung or Launois-Bensaude disease);

- Dercum's disease, also known as *adiposis dolorosa* or Ander's syndrome;

- Mesosomatic lipomatosis (LMS), also called Roch-Leri lipomatosis (5);

- Hibernomas, epidural lipomatosis and familial angiolipomatosis.

Of these lipomatous syndromes, LMS and Dercum's disease, the diagnosis of which is clinical, remain poorly described. Only isolated clinical cases or small studies aiming to report surgical treatment are mentioned in the literature (6-9).

Dercum's disease* is a very rare disease characterized by multiple, painful subcutaneous lipomas, occurring mainly on the trunk, and the proximal part of the arms and legs (10,11). The disease is often associated with obesity, asthenia and various neurological disorders, including depression and epilepsy (12). The pathophysiology of Dercum's disease remains unknown although various mechanisms have been suggested, such as autoimmunity, alterations in the metabolism of fatty acids, carbohydrates or hormones, previous infections (13) or abnormal lymphatic tissue (14). The majority of reported cases are sporadic, but a few apparently autosomal dominant familial cases have been reported (15-17). In addition to other multiple lipoma syndromes, the differential diagnosis includes fibromyalgia and lipedema (18). Treatment is symptomatic, mainly for analgesic purposes. Recurrence of lipomas after surgical removal is common.

Roch-Leri lipomatosis** is a disorder of adipose tissue proliferation characterized by the presence of generally painless, multiple, small lipomas, 2 to 5 cm in diameter, in the middle third of the body (forearms, trunk, thighs). They are easy to remove under local anaesthesia if not too numerous or confluent. No report of this partially forgotten syndrome has been available in PubMed since 1984, probably because it is usually considered harmless. Autosomal dominant cases have been reported but no gene has been identified and sporadic cases seem to be the most common (5).

These two mild disorders of Dercum's and Roch-Leri have piqued little clinical interest until recent findings on the heterogeneity of adipose tissue, its regenerative capacity, and its regulatory role in metabolism through the secretion of hormones and inflammatory mediators (19). A better understanding of these "benign" disorders could help to identify a currently lacking diagnostic biomarker and to better understand the mechanisms of these diseases and the pathophysiology of adipose tissue. Therefore, the

aim of the present study was to determine the clinical-immunological phenotype of Dercum's disease and LMS in comparison with control subjects.

*after Dr Dercum, an American neurologist (1856-1931); **after M. Roch, a Swiss internist (1878-1967) and A. Leri, a French doctor (1875-1930).

Patients And Methods

Study Design

This retrospective study was conducted at one university hospital over a decade from 2009 to 2019. All the patients referred to the institution's endocrinology and metabolism department with a final diagnosis of Dercum's disease or mesosomatic lipomatosis were included and compared with a control group of healthy subjects matched for age and gender who had been recruited from the NCT0178428 trial. This study protocol was approved by the relevant ethics committee, and all selected subjects gave their written informed consent to participate. Thus, this case-control study included men and women aged > 18 years from the following groups:

- Patients with Dercum's disease,
- Patients with Roch-Leri mesosomatic lipomatosis.
- Normal weight control subjects (BMI (Body Mass Index) > 18 kg/m2 but < 25 kg/m2)

Their clinical, metabolic and immune profiles were compared. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients and controls

A total of 76 patients were referred for a qualitative abnormality of adipose tissue over the ten-year period. After subjecting these patients to careful clinical and routine laboratory testing, those with a clinical phenotype suggestive of Dercum's disease or Roch-Leri-LMS were included.

Patients from the control group were excluded if they were aged < 18 years or fulfilled any of the following criteria: BMI > 25 kg/m^2; creatinine > 1.5 mg/dL; active cancer; excessive alcohol consumption; coagulation disorders; active autoimmune or chronic infection, including human immunodeficiency virus (HIV) and hepatitis C; treatment that might interfere with metabolic function, including estrogens and analogues (contraceptive pill, tamoxifen, etc.); and other medico-legal conditions (psychiatric disease; pregnant or breastfeeding women, etc.).

Clinical and biological data were collected from the patients' medical files at the time of assessment or, for the control group, from the NCT0178428 database.

Outcomes

Clinical parameters

Age, sex, height and body weight, and a family history of lipomatosis, diabetes mellitus or obesity were recorded, and BMI was calculated. Hypertension, defined as blood pressure > 130/85 mmHg (20) or the use of an antihypertensive drug, was recorded, as well as the use of lipid-lowering agents (such as statins, fibrates, ezetimibe), the use of antidiabetic treatments (such as lifestyle modification, metformin or any other antidiabetic drugs, including glucagon-like peptide-1 receptor agonists and insulin); and the use of analgesics and mood stabilizers.

The number and locations of lipomas were also recorded, as well as any previous history of lipoma surgery. The encapsulated nature of lipomas and the fibrous component of adipose tissue was studied by ultrasonography.

Metabolic parameters

- Fasting blood glucose (FBG), liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT]), triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels were measured using routine methods.
- Fasting insulin levels were measured by monoclonal immunoradiometric assay (Bi-INS-IRMA; Cisbio, Bedford, MA, USA) and fasting C-peptide using radioimmunoassay (RIA-coat C-peptide [Mallinckrodt France SARL, Paris, France], detection limit: 0.2 ng/mL).
- Leptin levels were measured by radioimmunoassay using commercial kits (Human Leptin RIA, EMD Millipore, Billerica, MA, USA). Intra- and inter-assay coefficients of variation (CVs) were < 8.5%.
- Diabetes and glucose intolerance were assessed by subjecting participants who were not already being treated for diabetes at inclusion to a 75-g oral glucose tolerance test (OGTT), which was interpreted according to the American Diabetes Association's criteria.
- HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) was calculated according to the formula: insulin (mIU/L) x glucose (mmol/L)/22.5.

Body composition parameters

- Body fat percentage was measured by dual-energy X-ray absorptiometry (DEXA; Lunar DPX-IQ, GE Healthcare, Chicago, IL, USA);
- Total and intra-abdominal fat, an estimation of subcutaneous and visceral fat, were measured from fat surface areas of 1-cm reconstructed slices of abdominal L4 magnetic resonance imaging (MRI),

Immunohematological parameters

The following were documented in the three groups:

- Personal history of immunoinflammatory disease (note that a history of autoimmune disease was an exclusion *criteria* for the control group).

- Blood count as well as platelets according to routine techniques.
- Lymphocyte immunophenotyping using flow cytometry (Navios flow cytometer, Beckman Coulter).

Statistical analysis

Quantitative variables were expressed as medians and first and third quartiles on graphs and as medians with minimum-maximum values in tables. Inter-group comparisons were performed using the Kruskal-Wallis or Mann-Whitney U tests. Qualitative values were expressed as proportions and compared between groups using the chi-square or Fisher's exact test according to validity conditions. Analyses were carried out with GraphPad Prism 6 software (GraphPad Software Inc., La Jolla, CA, USA). Any differences with p-values < 0.05 were considered significant.

Results

Characteristics of the groups

Overall, of the 76 patients referred for suspicion of lipodystrophy syndromes, 56 were excluded, whom 52 for other types of lipodystrophy syndromes and four because of insufficient data, death or persistent diagnostic doubt. Twenty lipomatosis cases were finally included:

- 9 patients with Dercum's disease (3 men and 6 women)

- and 11 patients with Roch-Leri lipomatosis (7 men and 4 women).

In addition, 18 healthy normal weight controls (10 men and 8 women) were included, resulting in a total of 38 patients (20 men and 18 females) (Figure 1-I).

Clinical characteristics of the Dercum's disease group

As shown in Table 1, the sex ratio was 2:1 for women and men, with a median age of 30 years and a BMI of 32.5 kg/m^2. The lipomas were mainly distributed on the thighs (67%), back (54%) and forearms (56%). Most patients (89%) had more than 10 lipomas (Figure 1-II). The ultrasonographic characterization showed that 88% of lipomas were encapsulated, 11% were fibrotic, and 11% were ecchymotic. Pain, which was an inclusion *criteria* for the Dercum's group, was present in 100% of cases, with 88% having paroxysmal pain and 12% with chronic pain. More than half of the patients (56%) had undergone at least one surgery, and the pathological analysis confirmed the diagnosis of lipoma in all cases. Res-pectively, 11%, 22% and 33% were treated for dyslipidemia, hypertension and diabetes before the diagnosis. For the pain, 33% of patients used level I and 56% level II analgesics; 36% received mood modulators (benzodiazepines and antidepressants) and 22% anti-epileptics. The proportion of immune function disorders in the personal history of the Dercum's patients was 22%. Eleven percent of the patients had a family history of first- degree lipomatosis.

Clinical characteristics of the Roch-Leri group

As displayed in Table 1, the sex ratio showed a male predominance, and patients had a median age of 31 years and a BMI of 30.8 kg/m^2. The painless lipomas were mainly located on the forearms (82%), thighs (73%) and abdomen (55%) (Figure 1-II). More than 80% of patients (82%) had more than 10 lipomas, which were always encapsulated, and 11% were fibrotic. Around half of the patients (54.5%) had undergone surgery for at least one lipoma, and the pathological analysis confirmed the diagnosis of lipoma in all cases. Respectively, 45%, 65% and 0% of patients were treated for dyslipidemia, hypertension and diabetes before the diagnosis. One case of diabetes was diagnosed with the OGTT (9% of the LMS group). None of the patients received long-term analgesics or mood stabilizing medications. The proportion of immune function disorders in the personal history concerned almost half of patients (45%). Around one-third of patients (27%) had a family history of first-degree lipomatosis.

Comparison of the Dercum's disease and the Roch-Leri groups

Clinical phenotype

The sex ratio differed between the Dercum's disease and LMS groups (p <0.05), with a predominance of men (63%) in the LMS group and of women (66%) in the Dercum's group. There was no difference between the lipomatosis groups with regard to age at the time of the first assessment, around 31 years for the two groups. The location of lipomas did not differ significantly between the two groups except for a higher number of lipomas on forearms/arms in the LMS *vs.* the Dercum's group (82% *vs.* 56%; p< 0.05). The frequency of patients with a number of lipomas above 10 (around 80-90%) and the percentage of patients who had had at least one lipoma surgery did not differ between the two groups despite the fact that lipomas were painful and required analgesics in Dercum's disease (Table 1).

Metabolic phenotype

There were no differences in the lipid, liver enzyme, fasting glucose, insulin, C-peptide, HOMA-IR and leptin levels between the two groups (Table 2). Body composition parameters did not differ between the groups. The prevalence of treated hypertension, diabetes or dyslipidemia was similar (Table 1).

Immunohematological phenotype

The proportion of immune system disorders, such as vitiligo and dysthyroidism, in the Roch-Leri group (45%) tended to be higher than that observed in the Dercum's group (22%), but the difference was not significant. Similarly, the blood cell count (hemoglobin, platelets, leukocytes) and the differential was similar between the Dercum's and LMS groups except for the number of basophils, which was significantly higher (2.7 fold) in the Dercum's than in the LMS group (p<0.001). Also, the lymphocyte subpopulation count showed that the LMS group had a significantly lower total CD 3$^+$ T lymphocytes levels and CD4$^+$/CD8$^+$ T lymphocytes subpopulations levels compared with the Dercum's group (p <0.05) (Table 3 and Figure 3).

Comparison of the Dercum's group with the healthy control group

Metabolic characteristics

Weight (p<0.05), BMI (p<0.01), systolic and diastolic blood pressure (p<0.05) and percentage of fat mass and intra-/total abdominal fat ratio (p<0.01) were significantly higher in the Dercum's group than the control group (Table 2 and Figure 2). Likewise, the levels of gamma-GT, fasting blood glucose, insulin, C-peptide, HOMA-IR, LDL-cholesterol and leptin were significantly higher in the Dercum's group than the control group (Table 2 and Figure 2). Age, triglycerides, HDL-cholesterol levels as well as liver enzymes did not differ between the Dercum's and the healthy control groups.

Immunohematological characteristics

The levels of platelets and circulating leukocytes were significantly higher in the Dercum's group than in the control group (Table 3). The leukocyte differential, and the levels of lymphocytes, monocytes, nuclear neutrophils, circulating eosinophils at diagnosis did not differ between the Dercum's and the control groups. Only the levels of circulating basophils were significantly higher (52 fold) in the Dercum's group compared with the control group (p<0.05). The lymphocyte subpopulation count did not differ between the Dercum's and healthy control groups except for circulating natural killer (NK) cells, which were significantly lower in the Dercum's disease group (p<0.05) compared with controls (Table 3 and Figure 3).

Comparison of the Roch-Leri -group with the healthy control group

Metabolic characteristics

Weight (p <0.05), BMI (p <0.01), systolic and diastolic blood pressure (p <0.05) and percentage of fat mass and intra-/total abdominal fat ratio (p<0.01) were significantly higher in the Roch-Leri group compared with the control group (Table 2 and Figure 2). Likewise, the levels of gamma-GT, fasting insulin, C-peptide, HOMA-IR and leptin were significantly higher in the Roch-Leri-group compared with the control group (Table 2 and Figure 2). Age, and levels of fasting blood glucose, lipids and liver enzymes did not differ between the Roch-Leri group and the healthy control group.

Immunohematological characteristics

The blood cell count and the leukocyte differential at diagnosis did not differ between the Roch-Leri group and the control group. The lymphocyte subpopulation count showed CD3^{+}, CD4^{+}, and CD8^{+} lymphocyte levels significantly lower (around 1.9 fold) in the Roch-Leri group compared with the control group (p<0.05) (Table 3 and Figure 3).

Discussion

The aim of this monocentric retrospective study was to improve the phenotyping of two rare forms of lipomatosis, Dercum's disease and Roch-Leri lipomatosis. The results suggest that lipomas occur on a common background of obesity and metabolic profile in the two diseases. Interestingly, the

immunohematological profiles were distinct, with an increase of basophil number in DD patient and T lymphocyte depletion with a trend to more immunoinflammatory diseases in LMS.

The initial classification of the two types of lipomatosis was driven by the current knowledge of the diseases, with the main diagnostic criteria being the presence of at least two lipomas: painless in the case of Roch-Leri lipomatosis and painful in Dercum's disease, with pain usually being the reason for consultation. This shows how difficult the diagnosis can be since it relies on clinical examination without specific markers for diagnostic confirmation. Taking into account these limitations, the first finding of this study is the apparent rarity of these syndromes since about one case of each type of lipomatosis was diagnosed each year in a department where a mean of 6,000 patients are admitted yearly. As lipomas are usually considered benign and can be quite small, they are not always mentioned by patients and many lipomas may go unrecognized if the lipomas are not troublesome. These observations are the first limitations of the present analysis in association with the retrospective design. In contrast, this study is the first comparative study to include a well-defined healthy control group and about 20 cases of lipomatosis, albeit this number is low. It is also the first to compare the immunohematological profile.

The clinical results of the present series are in concordance with the literature underlining the female predominance of Dercum's disease and the male predominance of Roch-Leri lipomatosis. In contrast, although the age of occurrence of LMS is similar to that mentioned in literature (5), the age of occurrence of Dercum's disease, which is very close to that of LMS in this study (around 30 years old), is discordant with current knowledge. Indeed, Dercum's disease is usually considered a postmenopausal disease, though at least one case has been reported in a child. Interestingly, this young age of occurrence in our study could argue for a specific rather than "degenerative" disorder. The disease could be possibly favoured by a genetic anomaly – at least in some patients - since 11% of Dercum's and 27% of LMS cases were apparently familial.

A very similar metabolic phenotype was found in the two lipomatosis groups, distinct from the control group. Indeed, there was a consistent finding of

- overweight, most grade II (30-35 kg.m^2) obesity, with a high leptin level, and a high percentage of body fat mass and visceral fat mass, as reflected by a significantly increased intra-/total abdominal fat mass ratio.
- hypertension with systolic blood pressure > 130 mmHg in all "lipomatosis" patients, despite antihypertensive treatment in 65% of LMS patients and 22% of patients with Dercum's disease.
- hyperinsulinism as demonstrated by significantly higher fasting insulin, C-peptide and HOMA-IR in the LMS and Dercum's groups compared with the control group, although fasting blood glucose was only significantly increased in the Dercum's group.

Of note was that the lipid profile was not significantly different in the lipomatosis groups compared with the control group. A tendency for hypertriglyceridemia is described in the literature (21). Nevertheless, in the present study, 11% of patients with Dercum's disease and nearly half of those with LMS (45%) were

treated with a lipid-lowering drug, which shows that dyslipidemia was initially present but controlled by treatment. In addition, despite these treatments and although not significant, triglyceride levels tended to be higher in the Dercum's group than in the LMS group, which itself also had higher values than the control group, perhaps in relation to a higher frequency of diabetes in the Dercum's group. The differences between the two groups concerning the expression of the metabolic syndrome at a young age (30 years old), with more diabetes in the Dercum's group and more hypertension in the Roch-Leri group, might be related to sex differences (30). In accordance with the metabolic phenotype, the AST and gamma-GT levels, which are potential markers of liver steatosis, also tended to be higher in the lipomatosis groups than the control group, especially in the Dercum's group though not significantly.

Ultimately, the analysis of the metabolic phenotype of lipomatosis syndromes shows its nearly constant association with obesity and metabolic syndrome, which raises the question of the role of this metabolic syndrome, especially obesity, in their genesis. Taking into account the well-known relationship between adipose tissue, insulin resistance and inflammation/immunity, we then considered the immunohematological phenotype of the two groups of lipomatosis compared with healthy normal-weight controls.

Interestingly, the two types of lipomatosis exhibited different blood cell count abnormalities compared with controls. The Dercum's group showed a significant increase in leucocytes and platelets, suggesting underlying inflammation, although CRP levels only tended to be higher in the lipomatosis groups (22). This profile of increased levels of leukocytes and platelets has been found to be associated with metabolic syndrome (23, 24). Intriguingly, basophils, which are the least common granulocytes, were also significantly increased in Dercum's disease compared with controls. Basophils have recently been shown to initiate and expand inflammation through the production of specific cytokines (interleukin-4) and proteases (serine proteases and mast cell protease 8 and 11). Basophil activation is associated with T helper 2 (Th2) immune responses (25, 26) and elicits microvascular hyperpermeability and leukocyte infiltration in affected tissues, leading to inflammation. Interestingly, basophil infiltrates are a marker of many human cutaneous diseases (27). In addition, mast cells are very similar to basophil granulocytes. Basophils leave the bone marrow already mature, whereas the mast cells circulate in an immature form, only maturing once in a tissue site. Both are granulated cells that contain histamine, serotonin and heparin. Increased peripheral serotonin is associated with obesity (28). Inhibition of peripheral serotonin synthesis and genetic deletion of serotonin synthesis by mast cells have been shown to prevent the development of obesity and insulin resistance, a pathway that need to be further investigated in Dercum's disease (29, 30).

In addition, a significantly lower number of NK cells was found in Dercum's disease. In mice models, NK cells remove unhealthy adipocytes and stimulate the differentiation of healthy adipocytes. Therefore, a low level of NK cells in adipose tissue could participate in a low level of adipose tissue remodelling, favouring inflammation and insulin resistance (31). Interestingly, NK cells and basophils are the key cells involved in priming and developing *in vivo* Th2 responses (32). The results of the present study then suggest that the underlying mechanisms of Dercum's disease could be mediated through a low level of

NK cells, which decreases fat remodelling and favours basophil activation. This could then contribute to chronic subclinical inflammation and pain. It is, however, difficult to know if these immune alterations found in blood are also present in adipose tissue and are the cause or the consequence of the metabolic syndrome. Their absence in the Roch-Leri group suggests that they might participate in the specific clinical presentation of Dercum's disease with its recurrent painful lipomas, which could correspond to inflammatory foci of adipose tissue.

Roch-Leri lipomatosis was associated with a different immune profile, which is only characterized by a significant decrease of total plasmatic CD3$^+$ T cells, and to a lesser extent of CD4$^+$ T helper/regulatory T cells and cytotoxic CD8$^+$ T cells. Interestingly, this group showed a relatively high proportion of patients with autoimmune disease. The association between lymphopenia and autoimmunity is recognized, but the underlying mechanisms are poorly understood (33, 34). A sex-specific adipose tissue imprinting of regulatory T cells has also been shown and could participate to these variations since a predominance of male was found in the LMS group (35). Nevertheless, due to the low number of patients studied, the results need to be regarded with caution, although a low-grade deficit of adaptive immunity could be considered.

Finally, the diagnosis of these orphan lipomatosis remains clinical at this time. The two syndromes associate multiple lipomas and a metabolic syndrome with obesity (BMI> 30 kg.m2), systolic blood pressure above 130 mmHg, hyperinsulinism, and for Dercum's disease only, a pain component. These criteria are not very discriminatory and so expose many patients to diagnostic wandering. This study shows that some cases could be familial. Associated pain, which is possibly related to an increase basophil number, and a low NK cell count could orientate the diagnosis towards Dercum's disease. The association of immune function diseases and a T lymphocyte deficit could support a diagnosis of a Roch-Leri lipomatosis. Nevertheless, these findings have to be confirmed on a larger number of patients. In Dercum's disease, QOL (Quality of Life) is impaired (12), a fact which is confirmed by the high level of use of analgesics and antidepressant drugs in the present study. A treatment targeting basophil activation such as omalizumab or benlizumab and perhaps serotonin synthesis (36), if confirmed by other studies, could be an option when available.

Conclusion

In conclusion, Dercum's disease and Roch-Leri lipomatosis associate multiple lipomas, which are painful in the case of Dercum's disease, and a metabolic syndrome with obesity. Dercum's disease is characterized by a moderate increase in platelets, leucocytes and basophils associated with a low NK cell count, whereas a decreased number of CD3, CD4, and CD8 was present in Roch-Leri lipomatosis. If confirmed, these findings could offer specific therapeutic opportunities.

Declarations

Funding

Disclosure of interest

Acknowledgments

Ethics approval and consent to participate: This study protocol was approved by the relevant ethics committee, and all selected subjects gave their written informed consent to participate.

Consent for publication: all selected subjects gave their written informed consent.

Availability of data and material: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions: ML, KLM and MCV designed the study, and collected, analyzed and interpreted the data. SB, GL and MLa. contributed to realize paraclinic examens and interpretation of these data. All authors read and approved the final manuscript.

References

1. Al Ghazal P, Grönemeyer LL & Schön MP -Lipomatoses. J Dtsch Dermatol Ges. 2018 ; 16 : 313–327

2. Vantyghem MC, Balavoine AS, Douillard C, Defrance F, Dieudonne L, Mouton F, Lemaire C, Bertrand-Escouflaire N, Bourdelle-Hego MF, Devemy F, Evrard A, Gheerbrand D, Girardot C, Gumuche S, Hober C, Topolinski H, Lamblin B, Mycinski B, Ryndak A, Karrouz W, Duvivier E, Merlen E, Cortet C, Weill J, Lacroix D, Wémeau JL -How to diagnose a lipodystrophy syndrome. Ann. Endocrinol. (Paris). 2012 ; 73 : 170–189

3. Brown RJ, Araujo-Vilar D, To Cheung P, Dunger D, Garg A, Jack M, Mungai L, Oral EA, Patni N, Rother K, Von Schnurbein J, Sorkina E, Stanley T, Vigouroux C, Wabitsch M, Williams R, Yorifuji T - The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. J Clin Endocrinol Metab. 2016; 101, 4500–4511

4. Sollier C, Capel E, Aguilhon C, Smirnov V, Auclair M, Douillard C, Ladsous M, Defoort-Dhellemmes S, Gorwood J, Braud L, Motterlini R, Vatier C, Lascols O, Renard E, Vigouroux C, Jéru I - Eur J Endocrinol

5. Muller R. *Dictionnaire médical de l'Académie de Médecine* – *Lipomatose multiple circonscrite mésosomatique de Roch-Léri*-1951 – 2020 version

6. Hansson E, Manjer J, Svensson H & Brorson H-Quality-of-life in patients with Dercum's disease–before and after liposuction. J Plast Surg Hand Surg- 2012; 46, 252–256.

7. Hansson E, Svensson H, & Brorson H- Liposuction May Reduce Pain in Dercum's Disease (Adiposis Dolorosa)- Pain Medicine 2011; 12: 942–952

8. Hansson E, Elmståhl S, Svensson H, Manjer J, Brorson H - Evaluation of measurement of fat mass reduction after liposuction in obese patients - Plast Surg Hand Surg. 2012;46(6):421-6.

9. Wollina U, Heinig B, Langner D, Nowak A - Juxta-articular adiposis dolorosa (Dercum's disease type IV): report of four cases and treatment by dermolipectomy- Wien Med Wochenschr. 2015;165(17-18):374-7.

10. Patel DA & Swan KG- Francis Xavier Dercum: a man for all seasons. Ann Clin Transl Neurol 2014; 1, 233–237

11. Hansson E, Svensson H & Brorson H - Review of Dercum's disease and proposal of diagnostic criteria, diagnostic methods, classification and management. Orphanet J Rare Dis 2012; 7, 23

12. Hansson E, Svensson H & Brorson H- Depression in Dercum's disease and in obesity: a case control study- Psychiatry. 2012;12:74.

13. Beltran K., Wadeea R. & Herbst K. L.-Infections preceding the development of Dercum disease. 2020; 19, e00682

14. Rasmussen JC, Herbst KL, Aldrich MB, Chinmay DD, Tan IC, Zhu B, Guilliod R, Fife CA, Maus EA and Sevick-Muraca EM- An abnormal lymphatic phenotype is associated with subcutaneous adipose tissue deposits in Dercum's disease. Obesity 2014; 22, 2186–2192.

15. Cantu JM, Ruiz-Barquin E, Jimenez M, Castillo L, Macotela-Ruiz E - Autosomal dominant inheritance in adiposis dolorosa (Dercum's disease). Humangenetik, 1973, 18, 89—91

16. Ledda RE, Raikes J, Crivelli P, Weichert I- Concurrent pulmonary embolism in female monozygotic twins affected by Dercum's disease. Oxf Med Case Reports, 2019,(1):123.

17. Campen R, Mankin H, Louis D, HiranoM, MacCollin M - Familial occurrence of adiposis dolorosa- J Am Acad Dermatol 2001;44:132-6.

18. Beltran K & Herbst KL -Differentiating lipedema and Dercum's disease. Int J Obes 2017; 41, 240–245.

19. Eckel J -Adipose Tissue: a major secretory organ. The cellular Secretome and Organ Crosstalk, 2018; 9-63

20. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, Jams WP, Loria CM, Smith SC Jr- International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, And Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society- Harmonizing the Metabolic Syndrome; 2009;120:1640-5

21. Oliveira Izar MC, Rodrigues da Fonseca HA, França CN, Arruda Machado V, dos Santos Ferreira CE, and Helfenstein Fonseca FA- Rare Presentation of Dercum's Disease in a Child with Abnormalities in Lipoprotein Metabolism. Arq Bras Cardiol 2018; 111, 755–757

22. Amine B, Leguilchard F, Benhamou CL - Dercum's disease (adiposis dolorosa): a new case-report. Joint Bone Spine. 2004; 71:147-9

23. Monserrat-Mesquida M, Quetglas-Llabrés M, Capó X, Bouzas C, Mateos D, Pons A, Tur J, Sureda A- Metabolic Syndrome is Associated with Oxidative Stress and Proinflammatory State. Antioxidants (Basel) 2020; 9, 236

24. Yang X-J, Tian S, Ma Q-H, Sun H-P, Xu Y, Pan C-W- Leukocyte-related parameters in older adults with metabolic syndrome - Endocrine 2020; 68: 312−319

25. Nakashima C, Otsuka A & Kabashima K - Recent advancement in the mechanism of basophil activation. J. Dermatol. Sci. 2018, 91: 3−8

26. Siracusa MC , Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, Wherry EJ, Jessup HK, Siegel LA, Kambayashi T, Dudek EC, Kubo M, Cianferoni A, Spergel JM, Ziegler SF, Comeau MR, Artis D - TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. Nature 2011; 477:229-33.

27. Otsuka A & Kabashima K − Mast cells and basophils in cutaneous immune responses- Allergy 2015; 70:131-40.

28. Kim JH, Noh S, Hur HJ, Sung MJ, Hwang JT, Park JH, Yang HJ, Kim MS, Kwon DY, Yoon SH - Metabolomic analysis of livers and serum from high-fat diet induced obese mice.J Proteome Res. 2011; 10:722−731.

29. Crane JD, Palanivel R, Mottillo EP, Bujak AL, Wang H, Ford RJ, Collins A, Blümer RM, Fullerton MD, Yabut JM, Kim JJ, Ghia JE, Hamza SM, Morrison KM, Schertzer JD, Dyck JR, Khan WI, Steinberg GR - Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis- Nat Med. 2015; 21:166-72.

30. Yabut JM, Desjardins EM, Chan EJ, Day EA, Leroux JM, Wang B, Crane ED, Wong W, Morrison KM, Crane JD, Khan WI, Steinberg GR - Genetic deletion of mast cell serotonin synthesis prevents the development of obesity and insulin resistance. Nat Commun. 2020;11:463

31. Park J, Huh JY, Oh J, Kim JI, Han SM, Shin KC, Jeon YG, Choe SS, Kim JB - Activation of invariant natural killer T cells stimulates adipose tissue remodelling via adipocyte death and birth in obesity. Genes Dev 2019, 33:1657-1672

32. Yoshimoto T -The Hunt for the Source of Primary Interleukin-4: How We Discovered ThatNaturalKiller T Cells and Basophils Determine T Helper Type 2 Cell Differentiation In Vivo. Front Immunol. 2018; 9:716-739

33. Jones JL, Thompson SAJ, Loh P, Davies JL, Tuohy OC, Curry AJ, Azzopardi L, Hill-Cawthorne G, Fahey MT, Compston A, Coles AJ - Human autoimmunity after lymphocyte depletion is caused by homeostatic T-cell proliferation, 2013; 110: 20200−20205

34. Tajuddin SM, Schick UM, Eicher JD, Chami N, Giri A, Brody JA, Hill WD, Kacprowski T, Li J, Lyytikäinen LP, Manichaikul A, Mihailov E & al -Large-Scale Exome-wide Association Analysis Identifies Loci for White Blood Cell Traits and Pleiotropy with Immune-Mediated Diseases. Am J Hum Genet.2016;99: 22-39

35. Vasanthakumar A, Chisanga D, Blume J, Gloury R, Britt K, Henstridge DC, Zhan Y, Torres SV, Liene S, Collins N, Cao E, Sidwell T, Li C, Spallanzani RG, Liao Y, Beavis PA, Gebhardt T, Trevaskis N, Nutt SL, Zajac JD, Davey RA, Febbraio MA, Mathis D, Shi W, Kallies A.Sex-specific adipose tissue imprinting of regulatory T cells. Nature. 2020 ; 579: 581-585.

36. Yabut JM, Crane JD, Green AE, Keating DJ, Khan WI, Steinberg GR - Emerging Roles for serotonin in Regulating Metabolism: New Implications for an Ancient Molecule. Endocr Rev. 2019; 40:1092-1107

Tables

Characteristics at diagnosis:	Dercum's (n=9)	LMS (n=11)	p
Clinical data			
Sex-ratio (M/F)	0.5 (3M/6F)	1.75 (7M/4F)	**0.005**
Age (years)	30.8 [16-50]	31.2 [18-68]	0.69
Weight (kg)	89 [58-98]	100 [55-142]	0.42
BMI (kg/m^2)	32 [27-59]	31 [25-35]	0.71
Spontaneous / induced pain (%; n/N)	100% (9/9) / 100% (9/9)	0% (0/10) / 20% (2/10)	**0.0001**
Number of lipomas > 10 (%; n/N)	89% (8/9)	82% (9/11)	>0.9
Encapsulated – fibrotic - ecchymotic (%; n/N)	89%-11% -11% (9/9)	100% -9% -9% (11/11)	>0.9
History of surgery (%; n/N)	56% (7/9)	54.5% (6/11)	>0.9
Lipomas sites			
Forearm/arm (%; n/N)	56% (5/9)	82% (9/11)	**0.042**
Back	56% (5/9)	27% (3/11)	0.87
Abdomen	44% (4/9)	55% (6/11)	0.99
Thigh	67% (6/7)	73% (8/11)	>0.99
Flank/ Lumbar fossa	44% (4/9)	36% (4/11)	>0.99
Legs	11% (1/9)	27% (3/11)	0.80
Other	44% (4/9)	9% (1/11)	**0.048**
Personal history			
Treated hypertension (%; n/N)	22% (2/9)	64% (7/11)	0.33
Diabetes (%; n/N)	33% (3/9)	9% (1/11)	0.28
Treated dyslipidemia (%; n/N)	11% (1/9)	45% (5/11)	0.16
Family history:			
History of lipomatosis	11% (1/9)	27% (3/11)	>0.9
History of diabetes	55% (5/9)	9% (1/11)	>0.9

Table 1: Main phenotypic characteristics of patients belonging to the Dercum's disease and Roch Leri lipomatosis (LMS) groups;

The number of patients studied was indicated only when at least one data point was missing: n: number of examinations performed/ N: total number of patients in the group

Metabolic characteristics	Dercum's (n=9)	LMS (n=11)	Controls (n=18)	p Dercum's vs. controls	p LMS vs. controls	p Dercum's vs. LMS
Clinical data:						
Age (years)	30.8 [16-50]	31.2 [18-68]	32.8[19-65]	0.35	0.16	0.69
Weight (kg)	89 [58-98]	100 [55-142]	69 [49-83]	**0.01**	**0,001**	0.42
BMI (kg/m^2)	32.5 [27-59]	31 [25-35]	22 [17-25]	**0.0005**	**0.0002**	0.71
Systolic Blood Pressure (mmHG)	130 [130-160]	140 [115-150]	115 [103-146]	**0.013**	**0.001**	0.42
Diastolic Blood Pressure (mmHG)	78.6 [60-90]	79.7 [70-95]	72.5 [68-89]	**0.04**	**0.04**	0.93
Metabolic data:						
Triglycerides (g/L)	1.22 [0.65-9.42]	1.37 [0.74-2.63]	0.87 [0.56-2.77]	0.07	0.83	0.98
HDL-c (g/L)	0.45 [0.34-0.55]	0.48 [0.41-0.82]	0.53 [0.38-0.72]	0.17	>0.99	0.15
LDL-c (g/L)	1.46 [0.83-2.72]	1.22 [0.91-1.87]	1.16 [0.92-1.4]	**0.03**	0.72	0.20
AST (IU/L)	27 [18-43]	25 [21-81]	22 [17-29]	0.05	0.09	>0.9
ALT (IU/L)	26 [14-75]	28,5 [11-78]	17 [10-31]	0.05	0.09	0.72
Gamma-GT (IU/L)	83 [58-125]	74 [30-139]	18.7 [11-28]	**0.0001**	**0.0001**	0.54
Fasting blood glucose (g/L)	1 [0.92-1.33]	0.98 [0.84-1.32]	0.86 [0.77-1.01]	**0.0028**	0.057	0.27
Fasting insulin (µIU/L; n/N)	8.1 [6.3-14-4] (7/9)	7.35 [6.3-35.8] (7/11)[a]	4.6 [1.2-9.2] (18/18)	**0.004**	**0.014**	0.68
Fasting C-peptide (ng/mL; n/N)	3.2 [2.46-4.33] (7/9)	2.57 [1.57-5.21] (7/11)[a]	1.75 [1-3.7] (18/18)	**0.016**	**0.04**	0.84
HOMA-IR (n/N)	2.67 [1.02-4.2] (7/9)	1.67 [1.4-11.6] (7/11)[a]	1 [0.25-2.18] (18/18)	**0.0008**	**0.02**	0.62
Leptin (ng/mL)	47.9 [6.7-224]	28.5 [13-110.8]	5.1 [4.1-16.1]	**0.003**	**0.0002**	>0.9
Anthropometric data:						
Fat mass estimated in DEXA (%; n/N)	37.1 [27.9-44.5] (6/9)	34.3 [31.5-42.8] (8/11)	22.9[17.9-34.9] (18/18)	**0.008**	**0.004**	>0.9
Intra/total abdominal fat ratio (n/N)	0.36 [0.20-0.98] (8/9)	0.31[0.24-0.6] (5/11)	0.19[0.10-0.60] (18/18)	**0.04**	**0.03**	0.87

Table 2: Main metabolic characteristics of patients belonging to the Dercum's disease and Roch Leri lipomatosis (LMS) groups compared to the control group;

a: exclusion of diabetic patients;

The number of patients studied was indicated only when at least one data point was missing: n: number of examinations performed/ N: total number of patients in the group

Characteristics at diagnosis	Dercum (n=9)	LMS (n=11)	Controls (n=18)	p Dercum *vs.* controls	p LMS *vs.* controls	p Dercum's vs. LMS
History						
Dysimmune disorders (%; n/N)	22% (2/9)	45% (5/11)	0% (18/18)	-	-	-
Paraclinical						
Hemoglobin (g/dL)	14.3 [12.5-15.4]	14.6 [12-15.4]	15 [12.1-17.3]	0.07	0.41	0.46
Platelets (10^3/mm^3)	266 [211-310]	220 [104-255]	210 [176-338]	**0.005**	0.39	0.10
Leukocytes (10^3/mm^3)	7.8 [5-9.1]	5.8 [5.2-9.8]	5.4 [4.3-11.1]	**0.02**	0.49	0.19
CRP (mg/L)	3 [3-18]	3 [3-10]	3 [3-4]	0.11	0.65	0.52
Leukocyte formula : (/mm^3)						
Lymphocytes	1939 [1100-2000]	1832 [600-2300]	1950 [1600-3300]	>0.9	0.72	0.63
Monocytes	500 [500-700]	400`[400-600]	400 [300-900]	0.21	> 0.9	0.33
Nuclear neutrophils	5200 [2600-10000]	3300 [2500-4600]	2800[1200-3260]	0.50	0.35	0.14
Eosinophils	150 [0-300]	100 [0-500]	100 [0-1600]	>0.9	0.26	0 .20
Basophils	52 [30-100]	19 [0-37]	0 [0-14]	**0.001**	0.57	**0.001**
Lymphocyte immune phenotyping (n/N)	(5/9)	(7/11)	(18/18)			
CD3+	1420 [1105-1904]	867 [513-1584]	1444[913-2607]	>0.9	**0.009**	**0.04**
CD4+	1255 [790-1710]	636.5 [328-922]	866 [367-1653]	0.23	**0.048**	**0.03**
CD8+	479 [454-788]	227[140-310]	546 [284-943]	>0.9	**0.014**	**0.007**
B Lymphocytes	204.5 [140-760]	227 [101-310]	211 [103-528]	>0.9	>0.9	0.93
NK Lymphocytes	207.5 [40-225]	210 [124-300]	292 [136-450]	**0.049**	0.31	0.53

Table 3: Main immunohematological characteristics of Dercum's disease and Roch-Leri lipomatosis (LMS) groups compared to the control group;

The number of patients studied was indicated only when at least one data point was missing: n: number of examinations performed/ N: total number of patients in the group
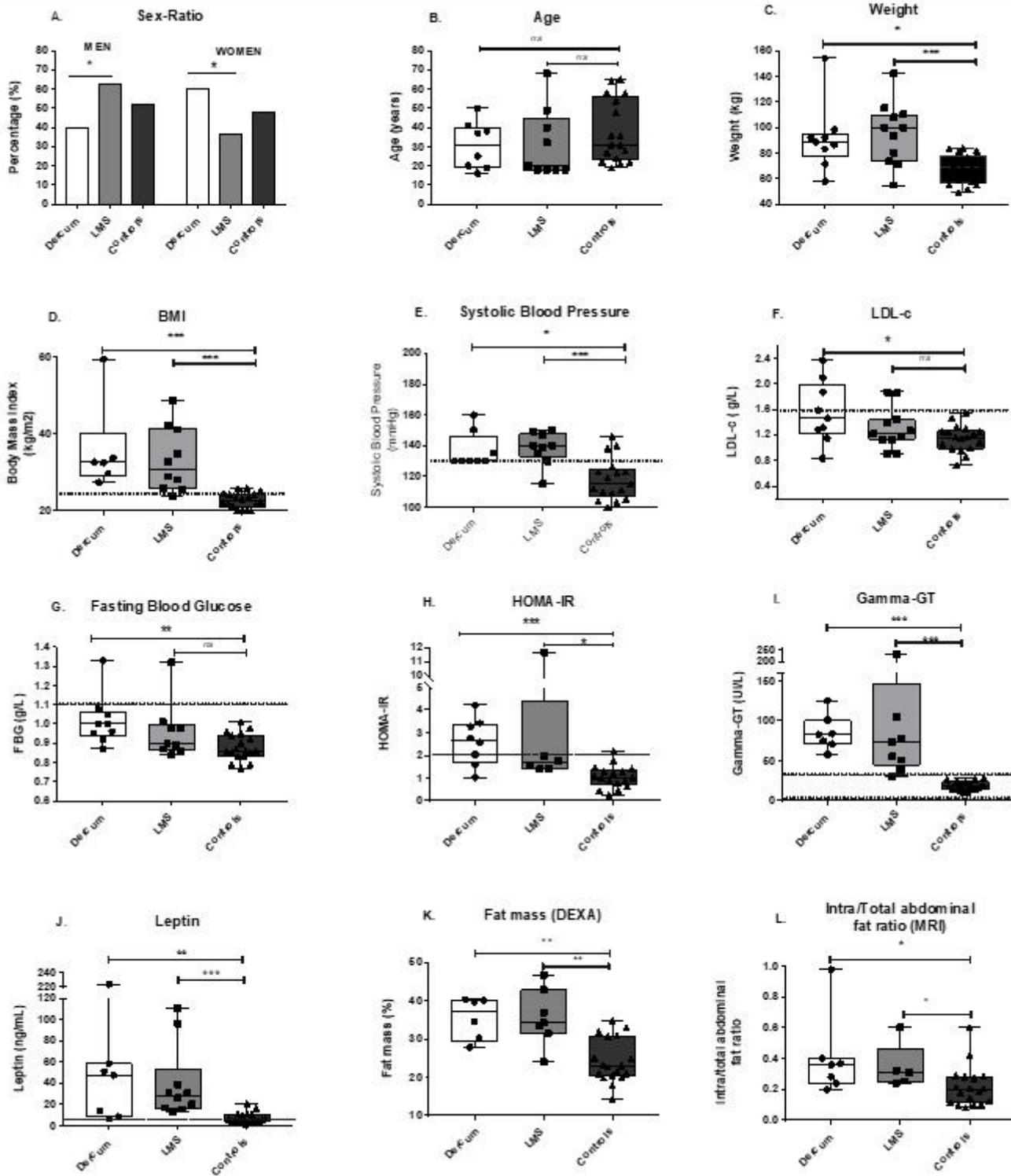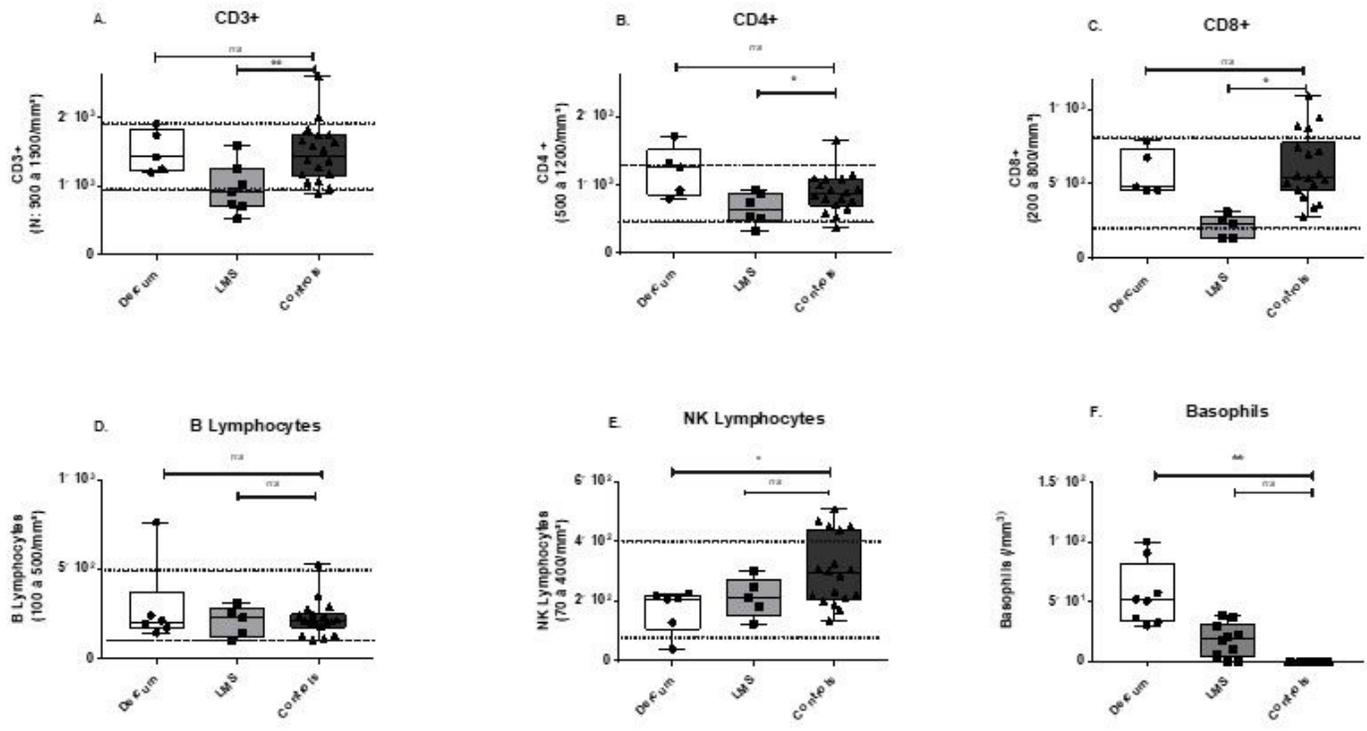
Figures
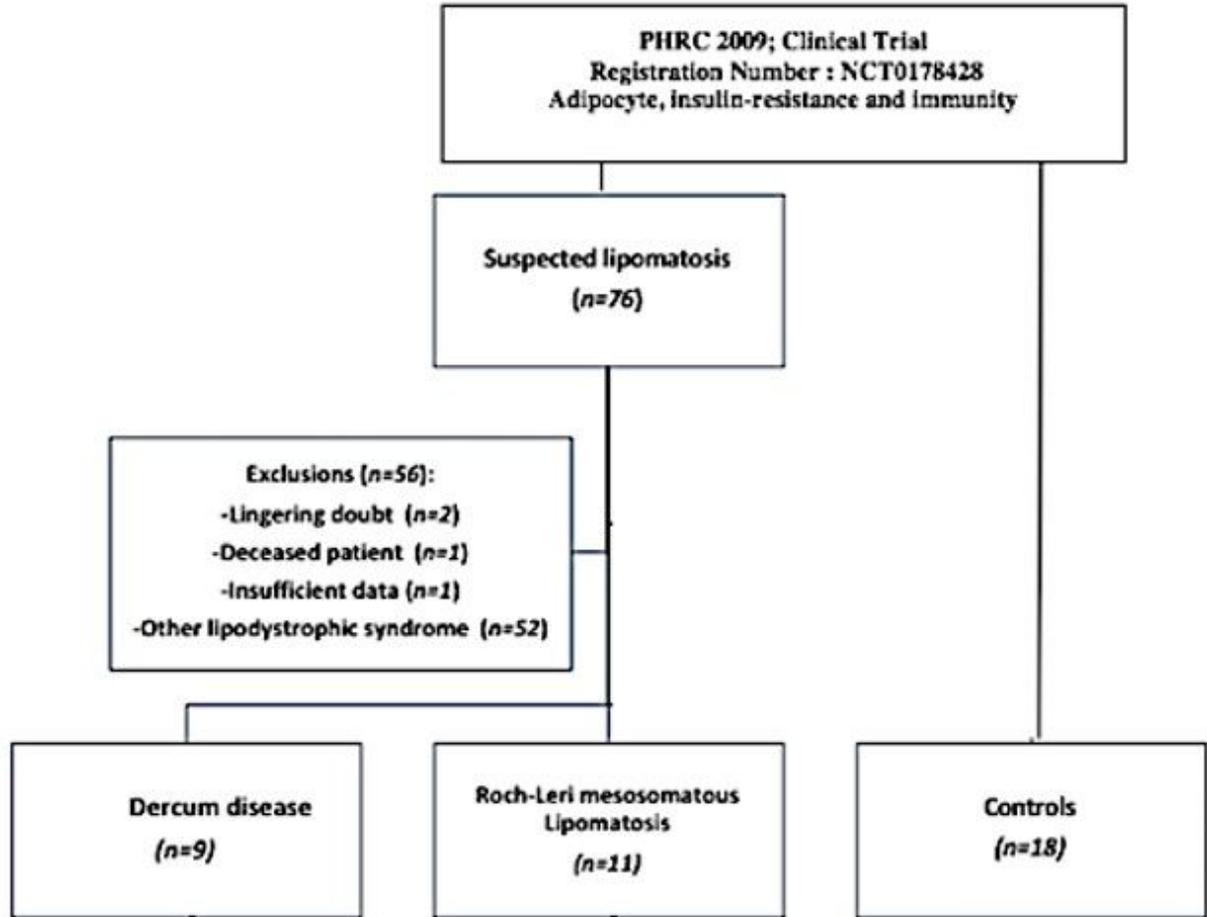
Figure 1

Patient enrollment; I: Patient enrollment flow-chart II: Iconography of Dercum's disease and Roch-Leri lipomatosis: On the left, patient with Dercum's disease: multiple encapsulated lipomas disseminated on the thighs associated with a pain component (a). On the right, patient with Roch-Leri LMS: multiple encapsulated lipomas, painless, disseminat-ed on the forearms (b).

Figure 2

Clinico-biological metabolic characteristics of Dercum's disease and Roch Leri lipomato-sis (LMS) compared with the control group. *: p<0.05, **: p<0.01, ***: p<0.001, ns: non significant ; p> 0.05 A, B, C, D, E: comparison of clinical characteristics between lipomatosis groups and the control group: A: sex-ratio; B: age (years); C: weight (kilograms) ; D: BMI (Body Mass Index) (kg/m2) E: SBP (Systolic Blood Pressure) (mmHg) F, G, H, I: comparison of biological metabolic characteristics between lipomatosis groups and the

control group: F: LDL-c (Low density lipoprotein cholesterol) (g/L); G: FBG (Fasting Blood Glu-cose) (g/L); H: HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) ; I: Gamma-GT (Gamma-Glutamyl Transferase) (ui/L) J, K, L: comparison of fat mass markers and distribution between lipomatosis groups and the con-trol group: J: Leptin (ng/mL) ; K: Fat mass, measured by DEXA (Dual x-ray absorptiometry) (%) ; L: Intra/Total abdominal fat ratio, measured by MRI (Magnetic Resonance Imaging)

Figure 3

Lymphocyte immunophenotyping of Dercum's disease and Roch Leri lipomatosis (LMS) compared with the control group; *: p<0.05, **: p<0.01, ***: p<0.001, ns: non significant p> 0.05 ABCDE: comparison of lymphocyte immunophenotype between lipomatosis groups and the control group: A: CD3 +: cluster of differentiation 3; B: CD4 +: cluster of differentiation 4; C: CD8 +: clus-ter of differentiation 8; D: Lymphocytes: B cells; E: NK: Lymphocytes: Natural Killer cells F: comparison of basophil lymphocytes between lipomatosis groups and the control group