Multiple Symmetric and Multiple Familial Lipomatosis.

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MULTIPLE SYMMETRIC and MULTIPLE FAMILIAL LIPOMATOSIS

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Short title: Clinico-biological aspects of rare lipomatoses

Word count: **3604 words -3 tables – 1 figure**

Key words: Lipomatoses, Multiple symmetric lipomatosis, Familial multiple lipomatosis,

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Disclosure of interest: The authors declare that they have no competing interest.

ABSTRACT:

Lipomas are the most common soft tissue tumors and are malignant in only 1% of cases. Lipomatosis is defined as the presence of multiple benign lipomas on the body, without lipoatrophy. Their impact on quality of life is significant. Different entities have been described such as symmetrical multiple lipomatosis (MSL), also called Madelung's disease and familial multiple lipomatosis (FML). MSL occurs preferentially in men (but also women) who are alcohol abuser. There are different subtypes of the disease, the most classic of which affects the upper body and the nuchal region with a buffalo hump appearance. A metabolic component with obesity is frequent. In contrast to Dercum's disease, there is no pain. SAOS, complications of the metabolic syndrome and of alcohol abuse including cancers, may be associated and should be screened. FML has been little described in the literature since Brodie's first report in 1846. FML occurs preferentially in the third decade but equally in women and men. Its autosomal dominant component is classically accepted with variable penetrance within the same family. Association with naevi, angiomas, polyneuropathies and with gastrointestinal comorbidities has been reported. Interestingly, and in contrast with most lipodystrophy disorders, the patients show an insulin sensitivity profile. A better understanding of the underlying pathophysiological mechanisms would open up avenues on therapeutic research, since treatments are only symptomatic to date.

INTRODUCTION

Lipomas are one of the most common soft tissue tumors in clinical setting. Only 1% of them are malignant. The term "lipoma" to describe these tumors was first used in 1709 [1-3]. The word “lipoma” comes from the ancient Greek λίπος - fat and ῶμα ỗma- tumor. The prevalence of lipomas is estimated around 2.1 per 1000 people, but these tumors are likely underreported because they are asymptomatic and do not always require medical care [4, 5]. Among abnormal fat distribution disorders, lipodystrophy syndromes are usually defined by a limited capacity of subcutaneous adipose tissue to store triglycerides causing metabolic abnormalities (insulin resistance, hypertriglyceridemia, fatty liver disease and polycystic ovary syndrome). Apart from these syndromes usually associated with partial or generalized lipoatrophy, lipomatosis is defined by the presence of several lipomas on the body, without lipoatrophy. Nevertheless, this classification is debated and lipomatosis are now often considered as part of lipodystrophy syndromes, raising new questions about the definition of the latter. Every “qualitatively abnormal” body fat distribution could be considered as a lipodystrophy syndrome, but the differential diagnosis with obesity, a “ quantitavively excessive” body fat accumulation, defined by a BMI > 30 kg/m^2 may become difficult, because of overlap. Indeed, lipomatosis, different subtypes of which are characterized by typical distribution patterns, usually occur without clear pathological explanations. They are considered to be benign, but some have a non-negligible impact on the quality of life [6]. The peak incidence occurs between the ages of 40 and 60 years. Lipomas are rare in children and occur

slightly more often in men compared with women. Lipomatosis might be isolated or syndromic. Different entities of isolated lipomatosis have been described such as:

- ✓ Familial multiple lipomatosis, a rare adipose disorder with multiple lipomas in subcutaneous fat. The penetrance is variable in the same family (FML),
- ✓ Multiples symmetrical lipomatosis most often linked to alcohol (Madelung or Launois-Bensaude disease) (MSL),
- ✓ Dercum's disease also called Adiposis Dolorosa or Ander syndrome, characterized by it pain component,
- ✓ Mesosomatic lipomatosis also called Roch-Leri lipomatosis, after M. Roch, Swiss internist doctor (1878-1967) and A. Leri, French doctor (1875-1930),
- ✓ Hibernomas, epidural lipomatosis and familial angiolipomatosis,

In contrast, some lipomatosis are part of a syndrome such as Proteus syndrome, Cowden syndrome, mutations in the *LMNA* gene, certain genetically determined multiple lipomatosis, and MERRF mitochondrial disease (Table 1)[7-26].

Throughout this review, we will present the available data on the 2 multiple isolated lipomatosis: symmetrical, better known as Launois-Bensaude syndrome or Madelung's disease and familial multiple lipomatosis. Dercum's disease and Roch-Leri mesosomatous lipomatosis have recently been reviewed and their main characteristics will just be reminded as differential diagnosis in Table 2 [27].

MULTIPLE SYMMETRIC LIPOMATOSIS: (Madelung's disease or Launois-Bensaude disease):

Madelung's disease, also called Launois-Bensaude disease or multiple symmetric lipomatosis (MSL), is an orphan disease listed by Orphanet (ORPHA:2398) and by the National Organization for Rare Disorders (NORD). Epidemiologically, the disease preferentially affects male adults, with an alcoholism history, although all ages and women can be affected [28]. The association with chronic alcohol abuse is identified in 60-90% of the reported cases, meaning that other causes may be identified [29]. All ethnic groups can be affected but the disease would be more frequent in Mediterranean area whereas Asian population seems rarely affected. The disease appears in mild to late adulthood (third to sixth decade). Prevalence of Multiple Symmetric Lipomatosis is estimated around 1:25,000 in a male Italian population and in a large German cohort [30]. The prevalence however varies according to geographical area and seems 10-fold lower in North of France (1/250 000), being in contrast not uncommon in women (50% of cases). Madelung's disease has many synonyms summarized in Table 2.

History:

The first description was made by Sir Benjamin Brodie, an English physiologist and surgeon, in 1846 and he found the condition to present as a " diffuse ruff-like fatty accumulation around the neck with grotesque distortion" [31]. In 1888, a first series of 33 clinical cases was reported by Otto Madelung, a

German surgeon [32]. In 1898, Pierre-Emile Launois, a French histologist and Raoul Bensaude, a French gastroenterologist, wrote the first detailed clinical study of MSL on 65 cases [33].

Pathophysiology:

Numerous hypotheses about possible triggers have been developed over time, such as psychological trauma [34], hypothalamic or pituitary lesion [35], or parathyroid glands tumors [36]. The exact cause of this lipomatosis is unknown, but environmental factors such as alcohol and genetic factors in some cases seem mainly involved.

Alcohol

Indeed, excessive alcohol intake could induce acquired immuno-inflammatory and mitochondrial dysfunction, a mechanism already described in some lipodystrophy syndromes (37). Alcohol is oxidized to toxic and carcinogenic acetaldehyde by alcohol dehydrogenase and further oxidized to a non-toxic acetate by aldehyde dehydrogenase (ALDH). There are two major ALDH isoforms, cytosolic and mitochondrial, encoded by *ALDH1* and *ALDH2* genes, respectively. The toxicity of alcohol on liver and adipose tissue may involve

- modification of microbiote [38]
- impairment of lipid metabolism [39]
- accumulation of acetaldehyde, inducing oxidative stress, inflammation, mitochondrial [40]
- dysfunction and epigenetic modifications [41]
- changes in enzymes and transporters, such as cytochrome P450 responsible for drug metabolism, in association with endocrine-disrupting chemicals, through the underlying liver disease [42,43]
- alterations of signaling pathways of adipokines such as FGF21[44]

Genetic alterations

As mentioned in Jeru's paper in the same issue of this journal, a few autosomal recessive forms of MSL have been identified, mainly involving the *MFN2* and *LIPE* genes through null variants They have been reported in less than 15 families worldwide for each gene.

Mutations in the *MNF2* gene coding for mitofusin 2 has been reported in MSL associated with lipoatrophy with the same pathogenic variant, p.Arg707Trp, in the homozygous or composite heterozygous state. The gene codes for an enzyme on the outer mitochondrial membrane, participating

in mitochondrial fusion and cell energy metabolism [45]. Its defect would induce unilocular adipocytes deficient in uncoupling protein 1 [UCP1] with enlarged and disorganized mitochondria, reduced mtDNA levels, increased expression of genes involved in mitochondrial oxidative stress, and a strong decrease in leptin and adiponectin expression [46]. *LIPE* gene encodes the hormone sensitive lipase, a key enzyme for triglyceride metabolism. It is expressed mainly in adipocytes but also in neurological tissue [47].

Besides these mendelian forms, studies suggest that MSL shows a detectable mitochondrial dysfunction such as multiple mitochondrial DNA deletions, pathogenic variants of the mitochondrial gene *MT-TK* or mitochondrial DNA mutations (pos.8344(A>G)), similar to those found in MERRF [48].

Moreover, in a family with myopathy and lipodystrophy syndrome, a MSL-like phenotypic appearance in non-dystrophic areas (accumulation of subcutaneous fat in the face, neck, axillae, and trunk but loss of subcutaneous fat from the lower extremities, and progressive distal symmetric myopathy during adulthood) has been associated with a homozygous Lipase E (LIPE)-mutation [47]. Angie Lindner & al., have identified Calcyphosine-like (*CAPSL*) as the single most interesting candidate gene in a four-generation family suffering from MSL [49]. In one case, new maternally transmitted m.8357T>C transition (mitochondrial DNA) was found as the etiological factor for the MSL [50]. Recently, the study of 6 cases of MSL revealed that the lipomatous tissue was a hyperplasic white adipose tissue secondary to an increase in stem cells and adipogenesis by up-regulation of AKT, CK2 and ERK1/2. These new genes could represent new therapeutic targets [51].

Therefore the pathophysiology of MSL remains poorly understood but seems related to a mitochondrial dysfunction either acquired, especially through toxicity of the alcohol byproduct acetaldehyde, or genetically determined or both.

Phenotype

Historically, two types of Madelung disease have been described, based on anatomic fat distribution. Type I is the most common form, characterized by neck location for tumors [52]. Fat distribution is symmetric and concentrated in the neck, shoulders, supraclavicular triangle and proximal upper limbs. In type 2, the neck and upper trunk are normal and fat depots are located on abdomen and thighs, reason why this subtype may be easily confused with common obesity [53]. Men would have more type 1 MSL and women more type 2 MSL [54]. In 1990-, a new classification was proposed by Donhauser, including four types: type 1—neck distribution; type 2—pseudo-athletic appearance; type 3—gynoid presentation and type 4-abdominal type [55]. More recently, D. Schilz & al., proposed a new classification based on a large German cohort of MSL patients which included 5 different subtypes (Ia: neck, Ib: neck, shoulder girdle, upper arms, Ic: neck, shoulder girdle, upper arms, chest, abdomen, upper and lower legs, II: hips, bottom, and upper legs, and III: general distribution skipping head, forearms, and lower legs) (Figure

1)[56]. These multiple classifications show the heterogeneity of the phenotypes and overlap between type 1 and 2 distribution of Enzi classification may occur.

The adipose tissue is symmetrically localized on the neck and trunk, giving the appearance of a "horse collar" also called "Madelung's collar", or "buffalo hump sign" [57], but also on the upper arms and/or thighs (Figure 2). In MSL, hyperplastic subcutaneous fat tissue is not surrounded by a pseudo-capsule. Fatty masses are mainly painless and distributed along vascular and muscular areas giving a "pseudoathletic" appareance in some cases. Other disorders are frequently associated with Madelung disease:

- a metabolic syndrome, with obesity, high triglyceride levels, type 2 diabetes [58], hyperuricemia and liver enzymes disturbances
- hypothyroidism and adipomastia [59].
- Early cognitive impairment or presenile dementia even without alcohol abuse [60, 61].
-Obstructive ventilatory disorders and obstructive sleep apnea syndromes, suggesting possible compression by lipomas [62-64].
-Bilateral involvement of the parotid and minor salivary glands in type 1 Madelung disease [65]. In addition, sialadenitis is sometimes the first symptom that leads to diagnosis.
- Finally, peripheral neuropathies (related to distal axonal demyelination) and dysautonomia (possibly responsible for sudden deaths) have been reported. Eight out of ten MSL develop polyneuropathy, which may be complicated with foot ulcers [66]. This neuropathy is usually associated to alcohol abuse and/ or diabetes. However, it has been suggested that alcohol is not the only cause of neuropathy, based on the lack of correlation between conduction velocities and alcohol consumption, the presence of neuropathy in abstinent patients with MSL, and the lack of sural nerve involvement, which tends to be surprisingly normal compared to the axonal degeneration and demyelination typically seen in alcoholic neuropathy. Polyneuropathy tends to be distal and symmetrical, with significant sensory and sometimes autonomic involvement of large fibers. In most cases, the onset of neuropathy is insidious [67,68].

Exceptional localizations are also reported in the literature such as bilateral and symmetrical breast lipomas similar to a gynecomastia [69], lipomas of the tongue [70,71] or bilateral orbital lipomas [72,73]. Rare associations have also been reported, including association with concomitant incarcerated femoral hernia [74] and with Bureau-Barrière syndrome, a peripheral neuropathy, with acro-osteolysis, and malum perforans pedis, in type III Madelung disease [75].

<u>Biological parameters:</u>

In addition to the aforementioned stigmas of metabolic syndrome [76,77], and despite the accumulation of fat in the subcutaneous tissue (and not the visceral tissue, usually considered as that one with a metabolic impact) [78], other abnormalities have been described, especially increase of lipoprotein lipase activity in adipose tissue, plasma hyperalphalipoproteinemia, and defective activity of adrenergic

receptors [79]. In a case-report, a hyperestrogenism was confirmed in association with normal testosterone levels and decreased dehydroepiandrosterone sulfate (DHEA-S) levels [80].

Diagnosis:

Diagnosis is mainly clinical. Often, the unsightly aspect is the only complaint of the patients. Different diagnoses need, however, to be ruled out:

- Common obesity, mainly in type 2 according to Enzi's classification,
- Liposarcoma [81],
- Cushing's syndrome, especially in type 1 of Enzi's classification with the "buffalo hump" appearance,
- Familial partial lipodystrophy, especially Dunnigan Syndrome (*LMNA* gene mutations)
- Familial angiolipomatosis
- Other lipomatosis syndrome
- Lymphoma

Paraclinical investigations:

Ultrasound examination is the first line investigation to confirm the fatty nature and benign characteristics of subcutaneous nodules; lipomas appear as symmetrical, non-encapsulated fatty deposits. Focal or whole-body magnetic resonance imaging (MRI) may be useful if there is any doubt [82]. It allows to analyze the exact distribution of fat, its encapsulation if any, a qualitative assessment of the degree of inflammation, fibrosis or necrosis, and the muscle or bone associated involvement. Biopsy of fatty masses may be carried out, especially if a liposarcoma cannot be excluded.

Prognosis:

The disease progresses rapidly in the first few years, after which progression usually slows down or stabilizes [83]. An excess of morbidity and mortality has been reported in these patients with sudden deaths without demonstrated coronary heart disease [51]. Despite rare, malignant transformations into liposarcoma has been reported, supporting the need of a scheduled medical re-evaluation of the adipose surface [84,85].

Therapeutic management:

Alcohol weaning is essential although there is no decay of the lipomatosis. Possible therapies include :

- ✓ Lipectomy/Lipoma Excision: Palliative surgery is performed for primarily cosmetic but also practical reasons in reason of the dressing issues. It allows histological analysis. Lipectomy and liposuction may be complementary in some cases [86],
- ✓ Liposuction: Brea-García & al., reported a total postoperative recurrence rate of 63%, nevertheless, up to 95% of patients experienced symptoms relapse after liposuction [87]

- ✓ Mesotherapy: The procedure consists of repeated injections of pharmacological and vitamin substances into the subcutaneous tissue, in order to reduce fatty tissue or cellulite. Phosphatidylcholine, pentoxifylline, hyaluronic acid, collagenase, etc. are used [88]. The indication must be given with caution given the possibility of secondary fibrosis, making liposuction difficult [89].
- ✓ Psychological support.
- ✓ Lifestyle measures, including exercise, could help to stop the progression of lipoma growth. However, some case reports do not mention any improvement or even a worsening of the symptomatology with weight loss.
- ✓ Management of comorbidities: diabetes, cirrhosis. It is necessary to evaluate the possibility of neoplasia secondary to alcohol (and often tobacco) consumption.

In summary, multiple symmetrical lipomatosis occurs preferentially in men (but also women) who are alcohol abuser. Rare genetic autosomal recessive forms have been reported. There are different subtypes of the disease, the most classical of which affecting the upper body and the nuchal region with a buffalo hump appearance. A metabolic component with obesity is frequent. In contrast to Dercum's disease, there is no pain component, but SAOS should be searched for as well as the well-known complications of the metabolic syndrome and of alcohol abuse including cancers.

FAMILIAL MULTIPLE LIPOMATOSIS (FML)

Familial multiple lipomatosis (FML) is a rare adipose disorder characterized by the presence of multiple lipomas (from a few lipomas to hundreds) in the subcutaneous fat. Penetrance is variable within the same family. FML is an orphan disease listed by Orphanet (ORPHA:199276). There is usually no pain. However, when the lipoma develops, it may cause local burning or itching. In addition, very transient paroxysmal pain is reported by some patients. Nevertheless, pain is never the first complain at difference with Dercum's disease , with which FML should not be confused The prevalence of FML is estimated to be 1:50 000. The ratio of females to males is usually close. Usually, lipomatosis appears in the third decade but may occur at any age even in children [90-92]. Confusion with MSL, also called symmetrical multiple lipomatosis, is common in the literature [93]. Familial multiple lipomatosis has also many synonyms mentioned in Table 2. About 175 FML cases have been reported in Pubmed.

History:

In 1846, Sir Benjamin Brodie reported the first case of a familial multiple lipomatosis. The hereditary aspect of FML was demonstrated in 1891 by Blashko [94] and by Alsberg in 1892 [95]. The distinction from Launois-Bensaude disease was made by Madelung himself, who described FML as an encapsulated multiple lipomatosis (Madelung's disease is a not-encapsulated lipomatosis) in 1888 [96].

Pathophysiology:

Inheritance is frequently autosomal dominant and different genetic abnormalities (*HMGA2* (High Mobility Group At-Hook 2) and *PALB2* (Partner And Localizer of BRCA2) are associated with the disease, without being considered as the cause [97,98]. The *HMGA2* gene, formerly named *HMGIC*, encodes a High Mobility Group (HMG) protein. HMGA2 plays an essential role in the genesis of adipose tissue, and numerous studies have shown the presence of *HMGA2* amplification in lipomas and also in malignant adipose tissue tumors [99]. *PALB2* is responsible of genome maintenance and *PALB2* gene mutations are associated with an increased risk of developing breast cancer because it can act synergistically with BRCA2 [100]. Further studies are needed to understand the precise mechanisms linking these genes with FML.

Phenotype

Lipomas are usually located on the trunk, lower back, arms and thighs. Rarely, they are located on the back or on the head. Clinical examination must rule out any symptom in favor of an associated neoplasia particularly by thyroid and breast palpation. Skin examination often shows naevi and capillary angiomas [101]. Association with brain anomalies and refractory epilepsy has been reported [102]. Polyneuropathy seems to be an associated symptom [103]. Association with gastroduodenal lipomatosis or celiac disease has been reported [96; 104-105]. A case-report describes an association with an EGIST (extra-gastrointestinal stromal tumors) which is also a rare familial disease [106], while another case reports on an association with mitral valve annular caseous calcification causing a severe mitral valve stenosis [107].

Biological parameters

At difference with most lipodystrophy disorders, FML is not associated with a metabolic syndrome. In 2002, the study of 83 members of the same FML family over three generations showed no abnormality of serum lipids, glucose levels, white blood cell count, hemoglobin, erythrocyte sedimentation rate and renal and hepatic function [108-109]. In 2013, the study of 4 brothers showed no insulin resistance after a 75 g OGTT assessment despite the accumulation of fat. Indeed, an increased insulin sensitivity was demonstrated compared to a control group. Euglycaemic hyperinsulinaemic clamp study in this FML family showed a borderline higher sensitivity to insulin secondary to a higher metabolic clearance of insulin [110].

The unique karyotypic analysis on tissue isolated from excised lipomas and peripheral blood was normal [111].

Diagnosis

Diagnosis is clinical. Often, the unsightly aspect is the only complaint of the patients. Misdiagnosis is common in most cases before the final diagnosis is made. Various differential diagnoses must be ruled out :

- RAS-MAPK pathway disorders: Type 1 neurofibromatosis, related to *NF1* gene mutations, Legius syndrome (see below), mutations in *SPRED1* gene, or Cowden disease (*PTEN* gene) (See table 1).
- Other types of lipomatosis, and specially Madelung's Disease. In FML, lipomas are discrete predominate on the extremities and their development are not associated with alcohol abuse (See Table 2).

Paraclinical investigations:

Ultrasound is the main investigation to confirm the fatty nature and benign characteristics of subcutaneous nodules; lipomas appear as encapsulated fatty deposits. Magnetic resonance imaging (MRI) and sometimes biopsy may be useful if there is any doubt, especially if a liposarcoma cannot be excluded.

Prognosis:

To date, no longitudinal study has specifically investigated the prognosis of people with familial multiple lipomatosis.

Therapeutic management:

There is little data available on the specific therapeutic management of FML; however, different approaches are available:

✓ Statin therapy: However, one case report describes a reduction in the size of lipomas after initiation of a treatment with statin (20 milligrams/day). After 4 years of treatment, the authors reported a 25% decrease in lipoma size compared to before statin therapy in a subject with a steady weight [112]. Prospective studies on a larger scale are however necessary to confirm the interest of this treatment.

✓ Psychological support,

✓ Liposuccion : the results are more esthetic than surgery of lipomas, which are associated with scars [113],

✓ Lipectomy/ Excision of lipomas with the possibility of minimal invasive approach because this approach had an excellent cosmetic result with minimal postoperative scarring [114],

✓ Lipolysis : a significant reduction of lipoma size after four injections of phosphatidylcholine (the detergent sodium deoxycholate, a component of injectable PDC, causing nonspecific lysis of cell membranes), at intervals of 6 to 8 weeks. However, no complete dissolution was observed in any lipoma [115]. Collagenase, deoxycholic acid, detergents have already shown their

effectiveness in reducing the size or destroying certain lipomas. However, prospective studies seem essential to confirm this possibility and the lack of side effects.

✓ Cryotherapy [116],

To summarize, FML has been little described in the literature since the first report by Brodie in 1846. Its autosomal dominant component is classically accepted with variable penetrance within the same family. Interestingly, it appears to be associated with a pattern of insulin sensitivity, but this needs to be confirmed by further studies. The gene(s) involved are not known yet.

CONCLUSION:

Lipomatoses are human diseases characterized by the accumulation of benign lipomas, associated in the case of Dercum disease only with a prominent pain complaint. Most of these lipomatoses has been discovered in the 19th century and have since been considered benign, raising little interest with only case reports or small series in literature. Most lipomatoses is not associated with specific biological markers and the differential diagnosis might be difficult especially because frequent overlap between the different syndromes [7,27,117,118]. However, recent data have highlighted the presence of a frequent metabolic syndrome associated with underlying obesity in MSL, with familial forms suggesting a genetic background in some rare cases, and sporadic forms mainly related to alcohol abuse. This last factor has been little studied in literature, despite the apparent specific effects in some adipocytes (arm, neck) but not all (forearms, calves) (Table 2) [119,120]. Metabolic syndrome and fat adipose disorders are frequently associated with inflammation, mitochondrial dysfunction, oxidative stress opening new diagnosis and therapeutic perspectives in the research field. Otherwise FSL appears as a familial form rather associated with insulin sensitivity. A better understanding of the underlying pathophysiological mechanisms would open up avenues of therapeutic research, since to date, treatments are only symptomatic, mainly involving surgery and treatment of the metabolic syndrome.

TABLE & FIGURE:

- **Table 1:** Differential diagnosis of lipomatosis,
- **Table 2:** Main epidemiological, clinical and biological data of the 4 main non-syndromic lipomatosis,
- **Figure 1:** Different classifications used in MSL,
- **Figure 2: Multiple symmetric lipomatosis or Launois-Bensaude syndrome:**

  A: Scapular proximal unencapsulated "leg sleeve" lipomas associated with adipomastia without facial adipose tissue accumulation despite obesity (type III Schiltz's classification),

  B: Cervical pseudocushingoid lipomatosis with adipomastia (type I Schiltz's classification),

Lipedema	Adipose tissue abnormality with a cuffing or "bracelet" effect to the wrists and ankles, but with no pain, Higher tissue water levels in lipedema [7-8],
Fibromyalgia	Diagnosis criteria [9]: • Painful symptoms > 3 months, • A Widespread Pain Index (WPI) of 7 and a Symptom Severity (SS) scale score of 5, or WPI between 3 and 6 and SS scale score of 9, • Elimination of any other cause of chronic osteoarticular pain. • Differential diagnosis with Dercum's disease
Panniculitis	Inflammation of the subcutaneous adipose tissue [10], Biopsy help to make diagnosis,
MSL, also called Madelung's disease	Upper body (shoulders, neck, head) and occurs preferentially in men with chronic excessive alcohol consumption, Multiple deletions of mitochondrial DNA, MERRF, LIPE, and MNF2 mutations [11],
Familial Multiple Lipomatosis	Lipomas mainly in the arms and legs from adolescence Autosomal dominant inheritance Abnormalities of the 12q13-15 region, which contains the HMGA2 gene and PALB2 gene mutation [12,13],
Type I neurofibromatosis	Neurofibromas related to mutations in the NF1 gene [14], Painless, except in case of degeneration,
MERRF syndrome	Rare mitochondrial disease characterized by myoclonic episodes, cerebellar ataxia, and myopathy [15], Multiple lipomatosis is associated in rare cases,
Roch Leri lipomatosis (RLML)	Non-painful benign lipomatosis affects young men [16,17],
Dercum's Disease (AD)	Painful benign lipomatosis with obesity affects adults [18-20]
Somatic mutations in the phosphatidylinositol/Akt/mTOR pathway ✓ **Proteus syndrome** ✓ **CLOVES syndrome** ✓ **Hemihyperplasia–multiple lipomatosis syndrome**	Disproportionate, asymmetric overgrowth of skin, bones, blood vessels, and fatty and connective tissue, related to a mosaic activating mutation in the AKT1 oncogene [21], Congenital pathology associating asymmetric lipomatous overgrowth, vascular malformation, epidermal nevi, scoliosis, and skeletal and spinal anomalies [22], Rare, overgrowth syndrome (progressive, asymmetrical, moderate hemihyperplasia) associated with multiple, slow-growing, painless, subcutaneous lipomas [23] ,

***PTEN* hamartoma tumor syndrome (PHTS)**	Mutations of the PTEN tumor suppressor gene, Multiple hamartomas, like SOLAMEN syndrome which includes segmental overgrowth, lipomatosis, arterio-venous malformation, and epidermal nevus [24],
Cushing syndrome	Facio-troncular fat accumulation, obesity, hypertension and diabetes mellitus,
Multiple Endocrine Neoplasia type 1,	*MEN1* gene mutation Lipomas or hibernomas, epidural lipomatosis, and familial angiolipomatosis [25, 26], Prevalence is unknown,

425

426 **Table 1: Differential diagnosis of lipomatoses:**

427 MERRF syndrome: myoclonic epilepsy with red ragged fibers; CLOVES syndrome: congenital,
428 lipomatous, overgrowth, vascular malformation, epidermal nevi, scoliosis, skeletal, spinal anomalies;
429 SOLAMEN syndrome: segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal
430 nevus.

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	Multiple Symmetric Lipomatosis [MSL]	Adiposis Dolorosa-Dercum disease [AD]	Roch Leri mesosomatous lipomatosis [RLML]	Familial Multiple Lipomatosis [FML]
Synomyms	-Launois-Bensaude disease, -Multiple symmetric lipomatosis, -Benign symmetric lipomatosis, -Familial benign cervical lipomatosis.	-Adiposis dolorosa juxta-articularis, -Rheumatism of the adipose tissue, -Morbus Dercum, -Adiposalgia -Ander's syndrome.	-Mesosomatic lipomatosis, -Discrete lipomatosis, -Roch lipomatosis, -Roch Leri syndrome, -Multiple circumscribed mesosomatic lipomatosis	-Circumscribed multiple lipomas, -Hereditary multiple lipomas, -Multiple subcutaneous lipomas, -Symmetrical lipomatosis.
Prevalence	Around 1:25,000	< 200 000 cases in the US	Unknown	Around 1:50,000
Epidemiology	-Adults, -Males, -Alcoholism, -Mediterranean regions (?).	-Adults, -Women, -Post-menopausal or younger, -All around the world.	-Adults, -Males, -30- years, -All around the world.	-Adults, -Sex ratio: 1, -< 30 years, -Autosomal Dominant.
First description	-1846 (Brodie B) -1888 (Madelung 0) -1898 (Launois PE & Bensaude R)	-1888 (Dercum FX)	-1846 (Brodie B) -Doctor Roch (1878-1967) & Doctor Léri (1875-1930)	-1846 (Brodie B) -1891 (Blaschko H) -1892 (Alsberg A)
Lipomas	Not encapsulated Painless "Buffalo hump sign" Five subtypes*:* -Type Ia,b,c : neck, shoulder girdle, upper arms, chest, abdomen, upper and lower legs, -Type II: hips, bottom, and upper legs, and -Type III: general distribution skipping head, forearms, and lower legs	Encapsulated, Painful, Hypertrophic adipose tissue Four types: -I: Generalized diffuse form -II: Lumpy form -III: Localized nodular form - IV: Juxta-articular form	Encapsulated, Painless, Numerous small lipomas, Middle third of the body,	Encapsulated, Painless, Local burning or itching when lipomas grow Rarely on the chief or on the back.
Accompanying symptoms	Metabolic syndrome, Hypothyroidism, Gynecomastia, Early cognitive impairment, Obstructive ventilatory disorders,	Metabolic syndrome, Depression, Digestive disorders, Hypertension, Asthenia, Shortness of breath, Repeated infections.	Metabolic syndrome *(Only our experience)*	Naevus, Capillary angiomas, Polyneuropathy, Gastro-intestinal comorbidity.

	Peripheral and dysautonomic neuropathy,			
Biological data	Dyslipidemia Diabetes Hyperuricemia Hepatic disorder	Dyslipidemia Diabetes Hepatic disorder Immuno-inflammatory profile with higher BSR, CH50. Modulation of some interleukins and a decrease of NK lymphocytes subpopulation *(Only our experience)*.	Dyslipidemia Diabetes Hepatic disorder hyperleptinemia, T Lymphocyte subpopulations decrease (CD3+, CD4+,CD8+)	Increase of insulin sensitivity?

Table 2: Main epidemiological, clinical and biological data of the 4 main non-syndromic lipomatoses

BSR : blood sedimentation rate ; NK: Natural killer

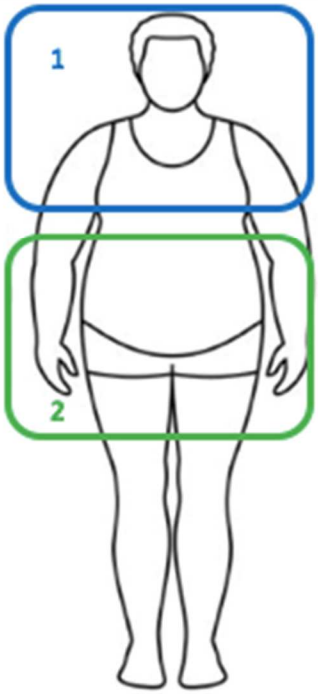
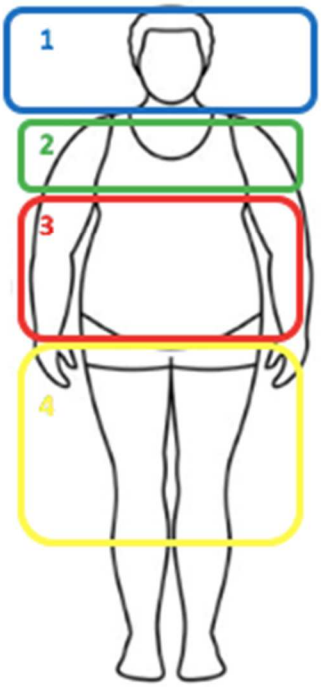
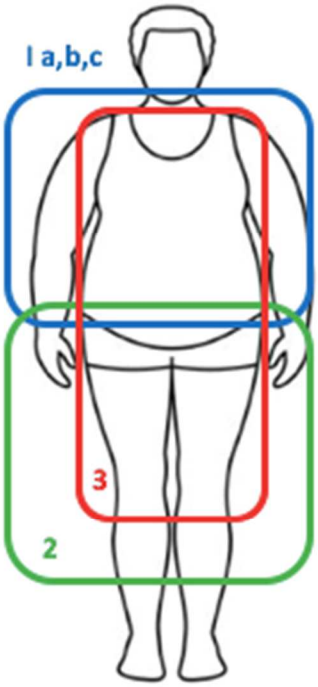
	Enzi's classification	Donhauser 's classification	Schiltz 's classification
Since :	1984	1991	2018
Subtypes:	Type 1 : Lipomas concentrated in the neck, shoulders, supra - clavicular triangle and proximal upper limbs.	Type 1: neck distribution;	Type I a,b,c : neck, shoulder girdle, upper arms, chest, abdomen, upper and lower legs,
	Type 2: neck and upper trunk are normal Fat depots located on abdomen and thighs,	Type 2: pseudo-athletic appearance	Type II: hips, bottom, and upper legs,
		Type 3: gynoid presentation	Type III: general distribution skipping head, forearms, and lower legs
		Type 4: abdominal type	
Topics:			

Figure 1- Different classifications used in MSL

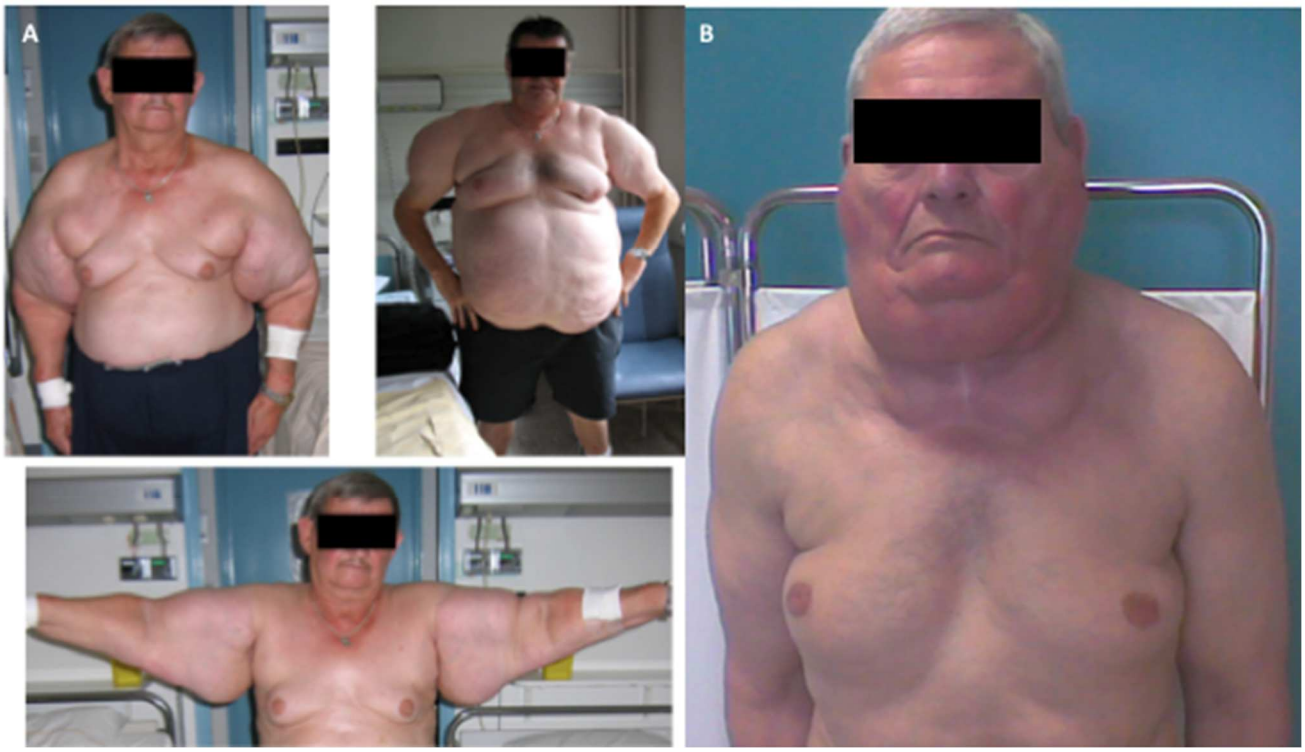


Figure 2: Multiple symmetric lipomatosis or Launois-Bensaude syndrome:

A: Scapular proximal unencapsulated "leg sleeve" lipomas associated with adipomastia without facial adipose tissue accumulation despite obesity (type III Schiltz's classification),

B: Cervical pseudocushingoid lipomatosis with adipomastia (type I Schiltz's classification).

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