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1 **MULTIPLE SYMMETRIC and MULTIPLE FAMILIAL LIPOMATOSIS**

2

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10

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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 ὄμα ὄμα- 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 " quantitatively excessive" body fat accumulation, defined by a BMI > 30 kg/m² 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

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

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

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

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

90

91 **MULTIPLE SYMMETRIC LIPOMATOSIS:** (Madelung's disease or Launois-Bensaude disease):
92 Madelung's disease, also called Launois-Bensaude disease or multiple symmetric lipomatosis (MSL),
93 is an orphan disease listed by Orphanet (ORPHA:2398) and by the National Organization for Rare
94 Disorders (NORD). Epidemiologically, the disease preferentially affects male adults, with an alcoholism
95 history, although all ages and women can be affected [28]. The association with chronic alcohol abuse
96 is identified in 60-90% of the reported cases, meaning that other causes may be identified [29]. All
97 ethnic groups can be affected but the disease would be more frequent in Mediterranean area whereas
98 Asian population seems rarely affected. The disease appears in mild to late adulthood (third to sixth
99 decade). Prevalence of Multiple Symmetric Lipomatosis is estimated around 1:25,000 in a male Italian
100 population and in a large German cohort [30]. The prevalence however varies according to geographical
101 area and seems 10-fold lower in North of France (1/250 000), being in contrast not uncommon in women
102 (50% of cases). Madelung's disease has many synonyms summarized in Table 2.

103

104 History:

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

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

110

111 Pathophysiology:

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

116 *Alcohol*

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

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

131 *Genetic alterations*

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

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

138 in mitochondrial fusion and cell energy metabolism [45]. Its defect would induce unilocular adipocytes
139 deficient in uncoupling protein 1 [UCP1] with enlarged and disorganized mitochondria, reduced mtDNA
140 levels, increased expression of genes involved in mitochondrial oxidative stress, and a strong decrease
141 in leptin and adiponectin expression [46]. *LIPE* gene encodes the hormone sensitive lipase, a key
142 enzyme for triglyceride metabolism. It is expressed mainly in adipocytes but also in neurological tissue
143 [47].

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

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

157

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

161

162 Phenotype

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

174 1)[56]. These multiple classifications show the heterogeneity of the phenotypes and overlap between
175 type 1 and 2 distribution of Enzi classification may occur.

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

182 - a metabolic syndrome, with obesity, high triglyceride levels, type 2 diabetes [58], hyperuricemia and
183 liver enzymes disturbances

184 - hypothyroidism and adipomastia [59].

185 - Early cognitive impairment or presenile dementia even without alcohol abuse [60, 61].

186 -Obstructive ventilatory disorders and obstructive sleep apnea syndromes, suggesting possible
187 compression by lipomas [62-64].

188 -Bilateral involvement of the parotid and minor salivary glands in type 1 Madelung disease [65]. In
189 addition, sialadenitis is sometimes the first symptom that leads to diagnosis.

190 - Finally, peripheral neuropathies (related to distal axonal demyelination) and dysautonomia (possibly
191 responsible for sudden deaths) have been reported. Eight out of ten MSL develop polyneuropathy, which
192 may be complicated with foot ulcers [66]. This neuropathy is usually associated to alcohol abuse and/
193 or diabetes. However, it has been suggested that alcohol is not the only cause of neuropathy, based on
194 the lack of correlation between conduction velocities and alcohol consumption, the presence of
195 neuropathy in abstinent patients with MSL, and the lack of sural nerve involvement, which tends to be
196 surprisingly normal compared to the axonal degeneration and demyelination typically seen in alcoholic
197 neuropathy. Polyneuropathy tends to be distal and symmetrical, with significant sensory and sometimes
198 autonomic involvement of large fibers. In most cases, the onset of neuropathy is insidious [67,68].

199 Exceptional localizations are also reported in the literature such as bilateral and symmetrical breast
200 lipomas similar to a gynecomastia [69], lipomas of the tongue [70,71] or bilateral orbital lipomas
201 [72,73]. Rare associations have also been reported, including association with concomitant incarcerated
202 femoral hernia [74] and with Bureau-Barrière syndrome, a peripheral neuropathy, with acro-
203 osteolysis, and malum perforans pedis, in type III Madelung disease [75].

204

205 Biological parameters:

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

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

212

213 Diagnosis:

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

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

224

225 Paraclinical investigations:

226 Ultrasound examination is the first line investigation to confirm the fatty nature and benign
227 characteristics of subcutaneous nodules; lipomas appear as symmetrical, non-encapsulated fatty
228 deposits. Focal or whole-body magnetic resonance imaging (MRI) may be useful if there is any doubt
229 [82]. It allows to analyze the exact distribution of fat, its encapsulation if any, a qualitative assessment
230 of the degree of inflammation, fibrosis or necrosis, and the muscle or bone associated involvement.
231 Biopsy of fatty masses may be carried out, especially if a liposarcoma cannot be excluded.

232

233 Prognosis:

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

239

240 Therapeutic management:

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

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

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

258

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

265

266 **FAMILIAL MULTIPLE LIPOMATOSIS (FML)**

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

277

278 *History:*

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

283

284 Pathophysiology:

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

294

295 Phenotype

296 Lipomas are usually located on the trunk, lower back, arms and thighs. Rarely, they are located on the
297 back or on the head. Clinical examination must rule out any symptom in favor of an associated neoplasia
298 particularly by thyroid and breast palpation. Skin examination often shows naevi and capillary angiomas
299 [101]. Association with brain anomalies and refractory epilepsy has been reported [102].
300 Polyneuropathy seems to be an associated symptom [103]. Association with gastroduodenal lipomatosis
301 or celiac disease has been reported [96; 104-105]. A case-report describes an association with an EGIST
302 (extra-gastrointestinal stromal tumors) which is also a rare familial disease [106], while another case
303 reports on an association with mitral valve annular caseous calcification causing a severe mitral valve
304 stenosis [107].

305

306 Biological parameters

307 At difference with most lipodystrophy disorders, FML is not associated with a metabolic syndrome. In
308 2002, the study of 83 members of the same FML family over three generations showed no abnormality
309 of serum lipids, glucose levels, white blood cell count, hemoglobin, erythrocyte sedimentation rate and
310 renal and hepatic function [108-109]. In 2013, the study of 4 brothers showed no insulin resistance after
311 a 75 g OGTT assessment despite the accumulation of fat. Indeed, an increased insulin sensitivity was
312 demonstrated compared to a control group. Euglycaemic hyperinsulinaemic clamp study in this FML
313 family showed a borderline higher sensitivity to insulin secondary to a higher metabolic clearance of
314 insulin [110].

315 The unique karyotypic analysis on tissue isolated from excised lipomas and peripheral blood was normal
316 [111].

317

318 Diagnosis

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

- 322 • RAS-MAPK pathway disorders: Type 1 neurofibromatosis, related to *NF1* gene mutations, Legius
323 syndrome (see below), mutations in *SPRED1* gene, or Cowden disease (*PTEN* gene) (See table
324 1).
- 325 • Other types of lipomatosis, and specially Madelung's Disease. In FML, lipomas are discrete
326 predominate on the extremities and their development are not associated with alcohol abuse
327 (See Table 2).

328

329 Paraclinical investigations:

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

334

335 Prognosis:

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

338

339 Therapeutic management:

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

- 342 ✓ Statin therapy: However, one case report describes a reduction in the size of lipomas after initiation
343 of a treatment with statin (20 milligrams/day). After 4 years of treatment, the authors reported
344 a 25% decrease in lipoma size compared to before statin therapy in a subject with a steady
345 weight [112]. Prospective studies on a larger scale are however necessary to confirm the interest
346 of this treatment.
- 347 ✓ Psychological support,
- 348 ✓ Liposuction : the results are more esthetic than surgery of lipomas, which are associated with
349 scars [113],
- 350 ✓ Lipectomy/ Excision of lipomas with the possibility of minimal invasive approach because this
351 approach had an excellent cosmetic result with minimal postoperative scarring [114],
- 352 ✓ Lipolysis : a significant reduction of lipoma size after four injections of phosphatidylcholine (the
353 detergent sodium deoxycholate, a component of injectable PDC, causing nonspecific lysis of
354 cell membranes), at intervals of 6 to 8 weeks. However, no complete dissolution was observed
355 in any lipoma [115]. Collagenase, deoxycholic acid, detergents have already shown their

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

358 ✓ Cryotherapy [116],

359

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

364

365 **CONCLUSION:**

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

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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]: <ul style="list-style-type: none"> • 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	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] ,
✓ Proteus syndrome	
✓ CLOVES syndrome	
✓ Hemihyperplasia–multiple lipomatosis syndrome	

<i>PTEN</i> hamartoma tumor syndrome (PHTS)	Mutations of the <i>PTEN</i> 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,	<i>MEN1</i> gene mutation Lipomas or hibernomas, epidural lipomatosis, and familial angioliipomatosis [25, 26], Prevalence is unknown,

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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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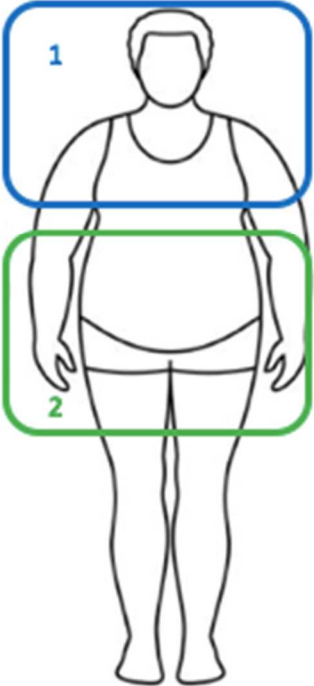
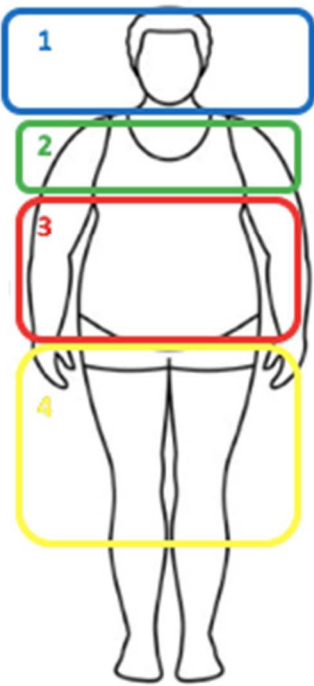
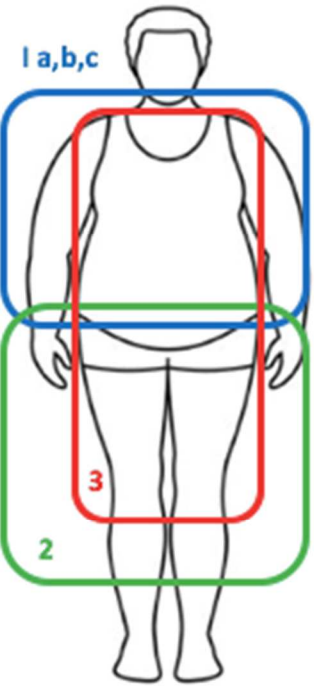
	Multiple Symmetric Lipomatosis [MSL]	Adiposis Dolorosa-Dercum disease [AD]	Roch Leri mesosomatous lipomatosis [RLML]	Familial Multiple Lipomatosis [FML]
Synonyms	-Launois-Bensaude disease, -Multiple symmetric lipomatosis, -Benign symmetric lipomatosis, -Familial benign cervical lipomatosis.	-Adiposis 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 (<i>Only our experience</i>)	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 (<i>Only our experience</i>).	Dyslipidemia Diabetes Hepatic disorder hyperleptinemia, T Lymphocyte subpopulations decrease (CD3+, CD4+,CD8+)	Increase of insulin sensitivity?

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

437 BSR : blood sedimentation rate ; NK: Natural killer

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	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	Type 2: pseudo-athletic appearance	Type II: hips, bottom, and upper legs,
	Fat depots located on abdomen and thighs,	Type 3: gynoid presentation Type 4: abdominal type	Type III: general distribution skipping head, forearms, and lower legs
Topics:			

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Figure 1- Different classifications used in MSL



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

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

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

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