Lipomatoses

Hippolyte Dupuis, Madleen Lemaitre, Arnaud Jannin, Claire Douillard, Espiard Stephanie, Marie-Christine Vantyghem

Annales d'Endocrinologie 85 (2024) 231–247

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Original article

Lipomatoses

Hippolyte Dupuis[a], Madleen Lemaitre[a,b], Arnaud Jannin[a,b], Claire Douillard[a], Stéphanie Espiard[a,b,c], Marie-Christine Vantyghem[a,b,c,d,*]

[a] CHU Lille, Endocrinology, Diabetology and Metabolism, 59000 Lille, France
[b] University Lille, 59000 Lille, France
[c] Inserm U1190, 59000 Lille, France
[d] Competence center PRISIS, France

INFO ARTICLE

Keywords :
Lipomatosis
Lipomas
Dercum disease
Madelung disease
Launois-Bensaude
Angiolipomatosis
Lipedema
Hibernoma
Proteus and Cowden syndromes
LMNA
MEN1
PIK3CA
MERFF
NF1

Mots clés :
Lipomatoses
Lipomes
Maladie de Dercum
Maladie de Madelung
Launois-Bensaude
Angiolipomatose
Lipoedeme
Hibernome
Syndrome de Protée
Syndrome de Cowden
LMNA
MEN1
PIK3CA
MERFF
NF1

ABSTRACT

Lipomatoses are benign proliferation of adipose tissue. Lipomas (benign fat tumors) are the most common component of lipomatosis. They may be unique or multiple, encapsulated or not, subcutaneous or sometimes visceral. In some cases, they form large areas of non-encapsulated fat hypertrophy, with a variable degree of fibrosis. They can develop despite the absence of obesity. They may be familial or acquired. At difference with lipodystrophy syndromes, they are not associated with lipoatrophy areas, except in some rare cases such as type 2 familial partial lipodystrophy syndromes (FPLD2). Their metabolic impact is variable in part depending on associated obesity. They may have functional or aesthetic consequences. Lipomatosis may be isolated, be part of a syndrome, or may be visceral. Isolated lipomatoses include multiple symmetrical lipomatosis (Madelung disease or Launois-Bensaude syndrome), familial multiple lipomatosis, the painful Dercum's disease also called Adiposis Dolorosa or Ander syndrome, mesosomatic lipomatosis also called Roch-Leri lipomatosis, familial angiolipomatosis, lipedema and hibernomas. Syndromic lipomatoses include *PIK3CA*-related disorders, Cowden/*PTEN* hamartomas-tumor syndrome, some lipodystrophy syndromes, and mitochondrial diseases, especially MERRF, multiple endocrine neoplasia type 1, neurofibromatosis type 1, Wilson disease, Pai or Haberland syndromes. Finally, visceral lipomatoses have been reported in numerous organs and sites: pancreatic, adrenal, abdominal, epidural, mediastinal, epicardial... The aim of this review is to present the main types of lipomatosis and their physiopathological component, when it is known.

1. Introduction

Lipomatoses are characterized by abnormal localized fat hypertrophy, without lipoatrophy, usually benign and with most of the time, typical distribution patterns. Lipomas (benign fat tumors, from Greek *lipos* = fat and *-oma* = tumor) are the most common component of lipomatoses but are sometimes considered a different entity when they are circumscribed [1]. Indeed, lipomatosis develop diffusely and are not surrounded by a fibrous pseudo-capsule, forming in some cases large areas of fat hypertrophy, whereas lipomas may be encapsulated or not. They can grow despite the lack of obesity. Because of the absence of lipoatrophy, lipomatoses are generally distinguished from lipodystrophy syndromes, which are characterized by limited capacity of subcutaneous adipose tis-

Abbreviations: ALT/WDLS, atypical lipomatous tumor/well differentiated liposarcoma

https://doi.org/10.1016/j.ando.2024.05.003

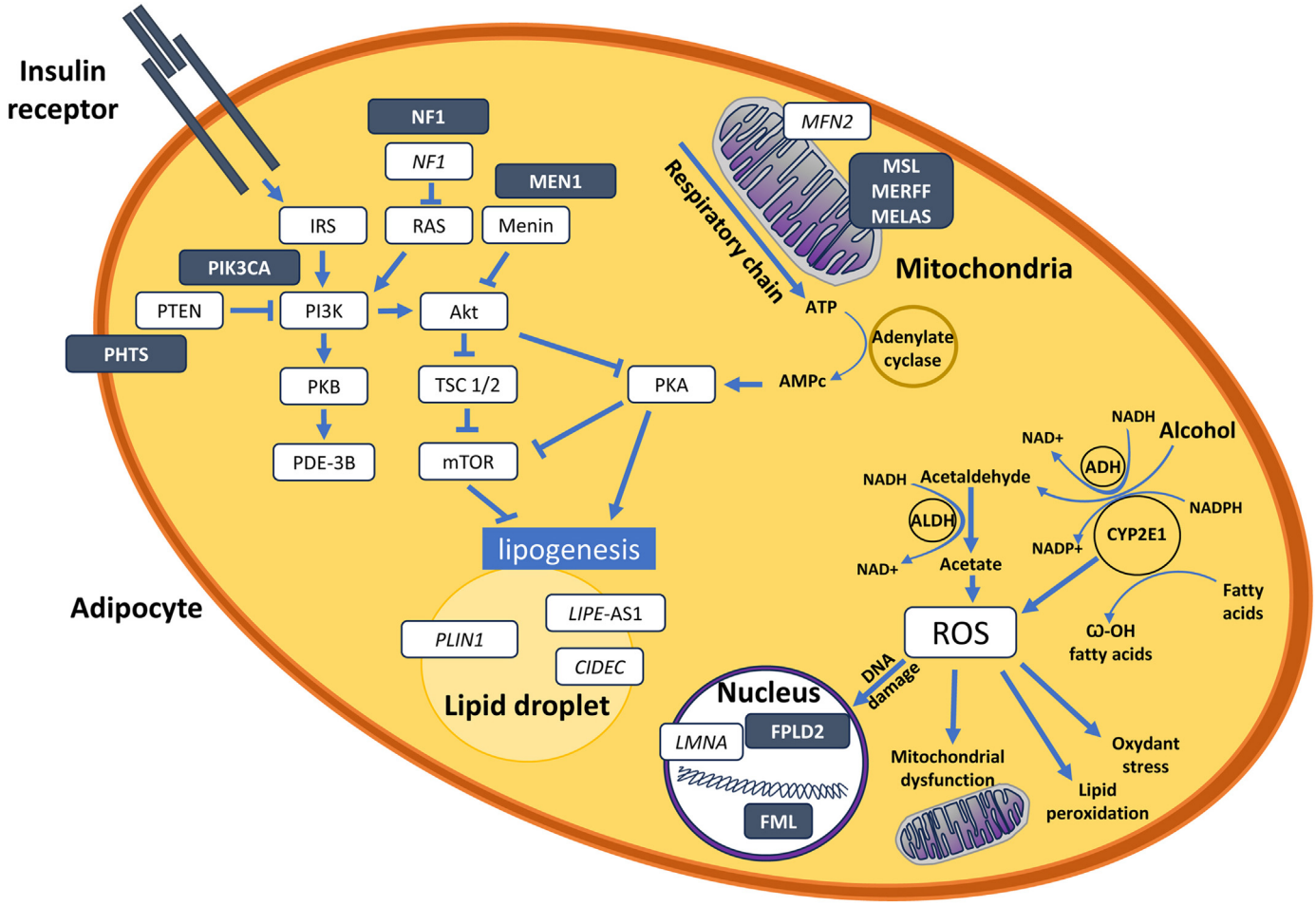

Fig. 1. Main physiopathological pathways involved in lipomatoses.

sue to store triglycerides causing notable metabolic abnormalities (insulin-resistance with diabetes, hypertriglyceridemia, fatty liver disease. . .) [2–4]. The degree of insulin resistance in lipomatosis is generally moderate, since there is no lipoatrophy, so no limitation of fat storage. Most of the time, metabolic syndrome is correlated to the degree of associated obesity. The impact of lipomatosis on quality of life is variable: lipomas may remain unnoticed, or induce functional discomfort to move, to dress or even to breathe, besides aesthetic and social consequences. Lipomatoses and their frontiers with obesity and lipodystrophy syndromes are sometimes difficult to define.

The prevalence of lipomas is estimated around 2 per 1000 people, but these tumors are likely underreported because they often are asymptomatic. Moreover, the definition of lipomatosis is larger than only lipomas. Considered as usually benign, and also due to their heterogeneity, lipomatoses have raised little scientific interest until recently (around 30 yearly references in Pubmed in 1975, 140 currently), whereas the number increased from 127 in 1975 to 551 in 2023 for "lipoma".

Knowledge concerning their pathological mechanisms will be reviewed when known for each entity, followed by a synthesis in section VII (Fig. 1).

The treatment, which will not be fully detailed, remains symptomatic in most cases (plastic surgery, liposuction, lipolysis, cryotherapy, analgesic therapy) associated to treatment of metabolic syndrome if present. Weight loss may improve symptoms especially in isolated lipomatosis but standard weight loss approaches, including lifestyle (diet, exercise), pharmacologic therapy, and even bariatric surgery, may be a failure due to tissue fibrosis. When an underlying mechanism has been identified, targeted treatments are indicated for each entity in the next sections.

CFRD, cystic fibrosis related diabetes
CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal and spinal syndrome
DC, Dercum's disease
ECCL, encephalocraniocutaneous lipomatosis
FAO, fibroadipose hyperplasia or overgrowth
FIB4, fibrosis 4 score
FIL, fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis
FML, familial multiple lipomatosis
FPLD, familial partial lipodystrophy syndrome
HHML, hemihyperplasia multiple lipomatosis
KTS, Klippel-Trenaunay syndrome
LIPE, lipase E
LON, lipomatosis of nerve
MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes
MEN1, multiple endocrine neoplasia type 1
MERRF, myoclonus epilepsy with ragged-red fibers syndrome
MRI, magnetic resonance imaging
MSL, multiple symmetrical lipomatosis
NF1, neurofibromatosis type 1
PNDS, Programme National de Diagnostic et de Soins meaning National Program for Diagnosis and Care
PHTS, *PTEN* hamartoma tumor syndrome
VFA/TFA, visceral abdominal fat/total abdominal fat.

* Corresponding author. Endocrinology, Diabetology and Metabolism, CHU Lille, 59000 Lille, France.
Adresse e-mail : mc-vantyghem@chru-lille.fr (M.-C. Vantyghem).

Table 1
Classification of lipomatoses.

Isolated lipomatosis	Syndromic lipomatosis	Visceral lipomatosis
–Multiple symmetric lipomatosis or Madelung disease or Launois-Bensaude syndrome –Familial multiple lipomatosis –Dercum's disease or *Adiposis dolorosa* or Ander syndrome –Mesosomatic (Roch-Leri) lipomatosis	–PIK3CA-related disorders (PRO, Proteus syndrome) –Cowden/PTEN hamartoma syndrome –Familial Partial lipodystrophy syndrome –Mitochondriopathies (MERRF, MELAS)	–Pancreatic lipomatosis –Adrenal and abdominal myelolipomas –Abdominal lipomatosis –Mediastinal lipomatosis –Spinal epidural lipomatosis
–Angiolipomatosis	–Multiple Endocrine Neoplasia type 1	–Cardiac steatosis and epicardial lipomatosis
–Lipedema – Hibernomas	–Neurofibromatosis type 1 –Wilson's disease –Pai syndrome –Encephalocraniocutaneous lipomatosis or Haberland syndrome	– Others (synovial. . .)

Lipomatous tumors may be classified into five different groups: simple lipomas, variant lipomas forms, heterotopic lipomas, infiltrating lipomas or lipomatosis, and finally hibernomas [5–8]. Nevertheless, we have chosen to rather classify lipomatosis according to the fact they are clinically isolated, syndromic, or visceral (Table 1).

Isolated lipomatoses include multiple symmetrical lipomatosis (Madelung or Launois-Bensaude disease; MSL), familial multiple lipomatosis (FML), the painful Dercum's disease (Adiposis Dolorosa or Ander syndrome), mesosomatic lipomatosis (Roch-Leri lipomatosis), lipedema, angiolipomatosis, and hibernomas.

Syndromic lipomatoses initially reported in Proteus, Cloves or Cowden syndromes, can benefit today from a molecular classification with variations in the *PIK3CA*, *LMNA*, *LIPE, MFN2,* mitochondrial genes such as MERRF syndrome, and some rarer genetic pathways such as *NF1*.

Finally, visceral lipomatosis has been reported in numerous sites: pancreatic, adrenal (myelolipoma), abdominal, epidural, mediastinal, epicardial, synovial and so on.

The aim of this work is to review the main types of isolated [7,8] and syndromic lipomatosis as well as visceral lipomatosis.

2. How to investigate lipomas and lipomatosis

2.1. Clinical diagnosis

Lipomas typically present as soft, solitary, painless, subcutaneous nodules that are mobile and not associated with epidermal change. A characteristic "slippage sign" may be elicited by gently sliding the fingers off the edge of the tumor (if the swelling does not slip under the palpating finger, it is rather a cyst than a lipoma; see https://www.youtube.com/watch?v=C3fO056zPzl). The lipoma may also become firmer if exposed to cold ("ice test").

Schematically, lipomatoses may be diagnosed:

- on inquiry: familial or acquired, unique or multiple, painless, or painful.
- on examination: unique or multiple, symmetrical, or not, isolated, or syndromic, made of well limited or confluent lipomas, more or less fibrotic, with sometimes an angiomatous component, associated or not to obesity and various clinical features such as neuropathy. . .
- subcutaneous or visceral, this last diagnosis resulting of an imaging done purposely because of symptoms of compression or performed for another cause leading to an incidental discovery. whatever the localization the distribution of fat and lipomas should be analyzed.
- imaging and biopsy may show encapsulated or not encapsulated lipomas, while histological studies may argue for white or brown adipocytes.

2.2. Paraclinical investigations:

Ultrasound examination is the first line investigation to confirm the fatty nature and benign characteristics of subcutaneous nodules; lipomas appear as symmetrical, fatty deposits. It may even be used for the diagnosis of deep pancreatic lipomatosis, even if MRI is usually preferred in these situations. Combining high frequency ultrasound (HFUS) with clinical examination can generally improve the diagnostic accuracy, as well as contrast-enhanced ultrasound (CEUS) to differentiate between lipoma and atypical lipomatous tumors based on tumor perfusion [9,10].

Focal or whole-body magnetic resonance imaging (MRI) [11] 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. Abdominal MRI may also help to quantify liver steatosis and whole and intra-abdominal fat distribution. Different techniques may be used:

- Traditional fat detection methods include inversion-recovery and chemically selective fat-suppression pulse sequences, with the former being less sensitive to field heterogeneity and less tissue specific than the latter.
- Chemical shift-based sequences, using the inherent resonance frequency difference between lipid and water to depict intracytoplasmic fat, is very useful for evaluating liver steatosis and lesions such as pancreatic focal lipomatosis.
- The signal from large amounts of fat can be suppressed by using a narrow radiofrequency pulse for selective excitation of fat protons (i.e., fat saturation imaging), a technique that increases image contrast resolution, and is especially useful for evaluating renal angiomyolipomas, adrenal myelolipomas, and liposarcomas.
- MR spectroscopy is a promising method for quantifying absolute liver fat concentration.
- New and evolving techniques include magnetization transfer and modified Dixon sequences.

Biphotonic absorptiometry and impedancemetry allow to quantify fat, muscle, water, and their distribution.

Multimodality imaging combining positron emission tomography with ^{18}F-fluorodeoxyglucose, computed tomography, xenon-enhanced computed tomography, to non-invasively detect functional and structural changes associated with the browning process is emerging, although still in research [12].

Biopsy of fatty masses may be carried out, especially if a liposarcoma cannot be excluded.

2.3. Biological investigations

There are no specific recommendations. Nevertheless, looking for metabolic syndrome with fasting blood glucose, C-peptide or insulin, glycated hemoglobin, cholesterol HDL and LDL, triglycerides, oral glucose tolerance test, and measuring markers of adipose tissue (leptin, adiponectin), liver enzymes, (markers of liver steatosis), blood cell count, a biological fibrosis score such as FIB4, and CRP to screen for any inflammation, seem important.

2.4. Other investigations to look for complications

Lipomatoses are heterogenous diseases and at difference with, for instance lipodystrophy syndromes, no recommendation to look for complications has been done. Nevertheless, screening for sleep apnea obstructive syndrome especially in Launois-Bensaude syndrome, may be of interest. Metabolic MRI can help to quantify liver steatosis and the relative distribution of visceral and total abdominal fat mass, a witness of insulin resistance. A non-invasive Fibroscan may indicate the level of liver fibrosis and the degree of steatosis. The presence or absence of metabolic syndrome will guide the cardiovascular assessment for its impact: thus, heart ultrasound and non-invasive heart ischemic screening may be indicated in metabolic syndrome. Excessive alcohol consumption or any specific complaints may also justify additional investigations. An electromyogram may be useful if a neuropathy is suspected.

3. Isolated lipomatosis

The main characteristics of isolated lipomatosis (MSL, FML, Dercum, mesosomatic, lipedema, angiolipomatosis, and hibernomas) are summarized in Table 2A.

3.1. Multiple symmetric lipomatosis (MSL; ORPHA #2398; OMIM#151800)

3.1.1. Diagnosis

All ethnic groups can be affected by MSL, generally between the third to sixth decade. MSL was first described as a "diffuse ruff-like fatty accumulation around the neck with grotesque distortion" followed by series reports of 33 to 65 cases. 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 (Fig. 2). A metabolic component with obesity is frequent. The disease progresses rapidly in the first few years, after which progression usually slows down or stabilizes. In contrast with what is currently admitted, it affects equally both sexes [13], even in Asian population, mainly in chronic alcohol abuse [14], and does not decrease with alcohol discontinuation. An excess of morbidity and mortality has been reported with sudden deaths without demonstrated coronary heart disease, possibly related to the toxic effect of alcohol on heart, or to unrecognized mitochondrial diseases which is another etiology. A neuropathy is frequent. Despite rare, malignant transformation into liposarcoma has been reported, supporting the need for a follow-up [15]. In addition to a frequent metabolic syndrome, neoplastic complications especially related to excessive alcohol and tobacco consumption should be screened as well as sleep apnea obstructive syndrome.

3.1.2. Physiopathology

Environmental factors such as alcohol, and genetic factors in some rare cases, seem mainly involved. Hazardous alcohol may act on liver and adipose tissue especially through modifications of microbiota, lipid metabolism, oxidative stress, inflammation, mitochondrial dysfunction, epigenetics, adipokines, enzymes and transporters, such as cytochrome P450 related to acetaldehyde accumulation [7]. A few familial forms of MSL have also been identified, generally associating besides the neuropathy, a myopathy in the context of mitochondrial diseases such as MERFF syndrome [16,17]. Other mendelian genetic causes have been reported, mainly involving the *MFN2* and *LIPE* genes through null variants in less than 15 families for each gene. They will be detailed in the syndromic chapter IV.3 and IV.4. The differential diagnosis may be challenging [16,17].

3.1.3. Treatment

Plastic surgery may improve quality of life, but recurrence is favored by resumption of alcohol consumption.

In summary, multiple symmetrical lipomatosis occurs preferentially in people who are alcohol abuser. Rare genetic forms have been reported. In contrast to Dercum's disease, there is no pain component. 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.

3.2. Familial multiple lipomatosis (FML; ORPHA #199276; OMIM#151900)

3.2.1. Diagnosis

Familial multiple lipomatosis is characterized by the presence of painless, multiple encapsulated lipomas (from a few lipomas to hundreds) in the subcutaneous fat usually located on the trunk, lower back, arms, and thighs. Only 200 FML cases have been reported in Pubmed, with no longitudinal study [7].

At difference with most lipodystrophy disorders, FML is not associated with a metabolic syndrome. Most of the time, lipomatosis appears in the third decade but may occur at any age even in children. Confusion with MSL is common.

3.2.2. Pathophysiology

Inheritance is frequently autosomal dominant, with variable penetrance. Different genetic abnormalities (*HMGA2* [High Mobility Group At-Hook 2], a gene involved in the genesis of adipose tissue, and *PALB2* [Partner and Localizer of BRCA2]) are associated with the disease, without being considered as the cause. Recently, a variant of a zinc-finger encoding domain of the *PRDM10* gene was shown in a novel disorder overlapping with Birt-Hogg-Dubé syndrome associating skin and mucosal lesions, renal cell carcinomas and extensive familial lipomatosis. Further studies are needed to understand the precise mechanisms linking these genes with FML [18].

To summarize, FML has been little described since the first report in 1846. Rather associated with insulin sensitivity, it is considered autosomal dominant with variable penetrance, but no gene has been identified yet.

3.3. Dercum's disease (ORPHA #36397; OMIM#103200)

3.3.1. Diagnosis

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 [8,19,20] (Fig. 3 left). The disease is often associated with obesity, asthenia, and various neurological disorders, including depression and epilepsy. Nevertheless, it is not certain that these disorders are related to the disease itself. In addition to other lipomatosis and obesity, the differential diagnosis includes fibromyalgia and lipedema.

Table 2A
Characteristics of the main isolated lipomatosis.

Lipomatosis type	Mechanism	Classical presentation	Comorbidities	Treatment
Isolated lipomatosis				
Multiple symmetric lipomatosis or Madelung disease or Launois Bensaude syndrome	−Alcohol abuse −Genetic factors (figuring in Table 2B and MERFF, MFN2, LIPE. . .see Table 2B) −Mitochondrial dysfunction?	−30-60 years − Location: neck, upper body, grotesque distortion	Higher morbidity and mortality − Coronary disease − Neoplasia related to alcohol − Sleep apnea obstructive syndrome − Rare malignant transformation	−Plastic surgery −Reoccurence if resumption of alcohol abuse
Familial multiple lipomatosis	−Autosomal dominant disease without identified gene (*HMGA2*? *PALB2? PRDM10*?)	−30 years −Location: trunk, lower back, arms and thighs	No metabolic syndrome	−Possible surgical resection
Dercum's disease or *Adiposis dolorosa* or Ander syndrome	−Unknown: Lipid alteration? Previous infections? Lymphatic disorder? Basophil activation?	−Women −Painful deep subcutaneous lipomas located on the trunk and proximal members. −Three main subtypes: Type I: neck, shoulder girdle, upper arms Type II: hips, bottom, and upper legs, and Type III: general distribution skipping head, forearms, and lower legs	− Obesity − Neurological disorders (epilepsy, depression)	− Histamine 1/2 receptor blockers − Non-steroidal anti-inflammatory − Flavonoids (quercetin, pycnogenol) − immunosuppressants (suni-, tofaci-, ima-tinib. . . used in mastocyte disorders) −Pain reoccurs after surgery
Mesosomatic (or Roch-Leri) lipomatosis	−Unknown −Sometimes familial −Adaptive immunity disorder?	−Painless, multiple, small (2–5 cm) lipomas located between "breast and knees".	− Obesity − Metabolic syndrome − Autoimmune diseases?	Weight loss? Surgical resection?
Angiolipomatosis	−Sporadic > inherited (no identified gene) −Microthrombi?	−Men- sometimes painful -Unique or multiple nodules located on the arms and trunk with angiomatous component		Tricyclic antidepressant?
Lipedema or *Lipohyperplasia dolorosa*	−Unknown: Polygenic susceptibility? Hormonal disorders? Lymphatic or microvascular?	−Women (almost exclusively) −BMI most of the time > 35 −Disproportionate ± painful limbs (butt, thighs, calves; never feet and hands	−Psychological distress	Weight loss? Plastic surgery?
Hibernomas	−4 types according to the proportion of brown fat (UCP1) −Reciprocal translocations of chromosome 11q	−Mean age: 38 −Thigh, shoulder, and back −Sometimes atypical location (bone, breast. . .) FDG-PET uptake	−May be association with MEN1	Surgery

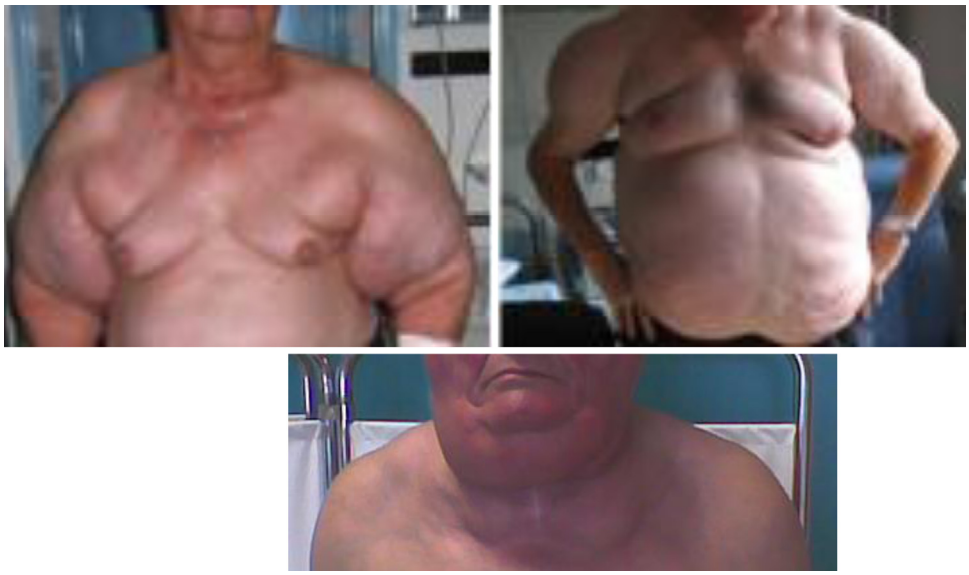

Fig. 2. Multiple symmetric lipomatosis: top: most frequent form affecting the upper part of the body; bottom: affecting only the neck.

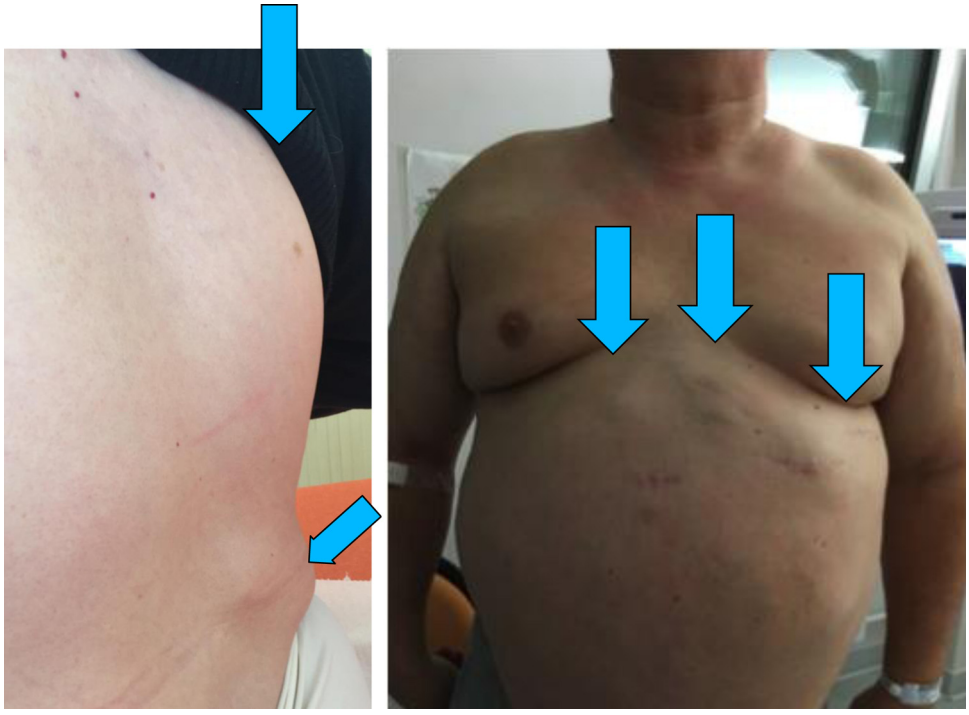

Fig. 3. Left: Dercum disease; right: Roch-Leri or mesosomatic lipomatosis.

3.3.2. Physiopathology

The pathophysiology of Dercum's disease remains unknown although various mechanisms have been suggested, such as autoimmunity, lipid alterations, previous infections, or abnormal lymphatic tissue. Most reported cases are sporadic, but a few apparently autosomal dominant familial cases have been described. Recently, a study comparing metabolic and immunohematology characteristics in 9 cases of Dercum disease, 11 Roch and Leri lipomatoses, 18 lean and 8 obese controls, showed a common background of obesity and metabolic phenotype, but a distinct immune-hematological profile in Dercum and Roch-Leri lipomatoses. The Dercum's group was characterized by increased levels of leukocytes and platelets, already reported in metabolic syndrome, and a specific increase of basophils on the one hand, with a lower number of Natural Killer (NK) cells on the other hand, compared with lean, but also obese controls. Basophil cells, very similar to mast cell, may expand inflammation, in association with T helper 2 (Th2) immune responses [21]. Both cell types contain serotonin, increase of which is associated with obesity [22,23]. Besides, the decrease of NK cells, which are usually dedicated to the removal of unhealthy adipocytes with a stimulation of proliferation, could participate in a low adipose tissue remodelling, favouring inflammation and insulin resistance.

3.3.3. Treatment

Treatment is currently symptomatic, and mainly analgesic. Recurrence of lipomas after surgical removal is common. but targeting mast cells and serotonin synthesis could deserve a trial.

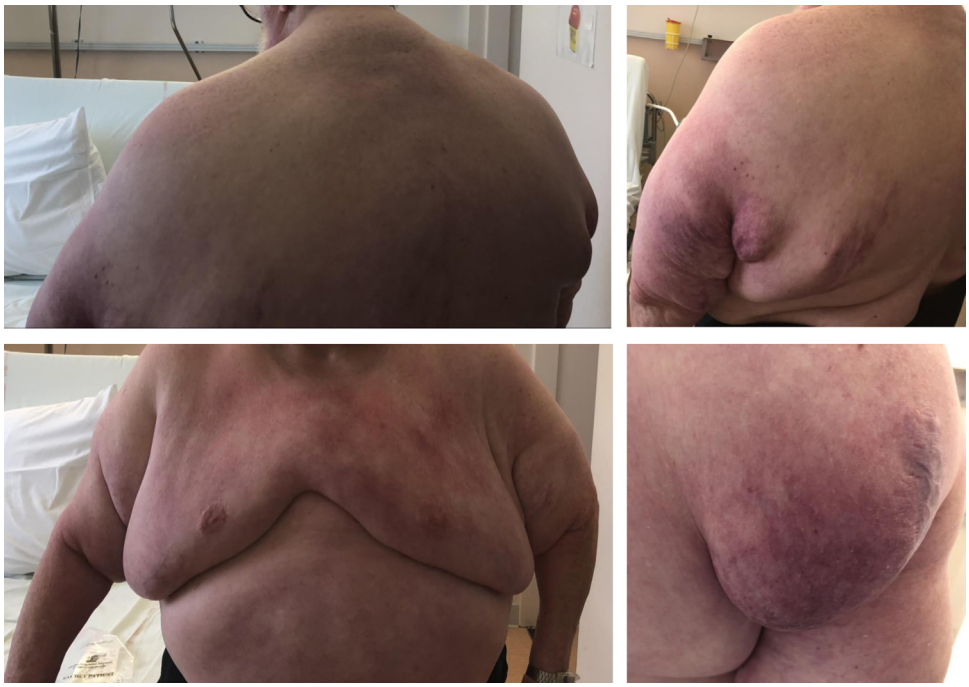

Fig. 4. Angiolipomatosis.

Reducing the burden of mast cells may involve histamine 1 and/or 2 receptor blockers, montelukast, non-steroidal anti-inflammatory drugs, antihistaminergic bioflavonoids such as quercetin or pycnogenol, and possibly powerful immunosuppressive drugs such as sunitinib (used for mastocytosis), or tofacitinib or imatinib (used for mast cell activation syndrome). Note that these last suggestions have not be tested in a randomized study and may show serious side effects.

To summarize, Dercum disease shows a background of obesity and metabolic phenotype, with a distinct immunohematological profile characterized by a low level of NK cells, favouring basophil activation, chronic subclinical Th2 inflammation and recurrent painful lipomas which may correspond to inflammatory foci of adipose tissue. These findings could offer specific therapeutic opportunities.

3.4. Mesosomatic (Roch-Leri) lipomatosis (ORPHA#529)

3.4.1. Diagnosis

Roch-Leri lipomatosis, characterized by the presence of generally painless, multiple, small lipomas, 2–5 cm in diameter, in the middle third of the body (forearms, trunk, thighs), has raised little scientific interest because it is considered harmless (Fig. 3 right).

3.4.2. Physiopathology

Autosomal dominant cases have been reported but no gene has been identified and sporadic cases seem to be the most common [8]. In a recent study [19], Roch-Leri lipomatosis was associated to the same metabolic phenotype as in the Dercum's group, but in contrast to lean and Dercum controls, Roch-Leri lipomatosis was characterized by a significant decrease of blood $CD3^+$ T cells, and to a lesser extent of $CD4^+$ T helper/regulatory T cells and cytotoxic $CD8^+$ T cells, a profile already reported in overweight subjects [24]. Also, this immune profile seems associated with a relatively high proportion of Roch-Leri patients with autoimmune disease (a type of disease also reported to be associated with lymphopenia). 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.

To summarize, as for Dercum disease, mesosomatic lipomatosis shows a background of obesity and metabolic phenotype, but a distinct immune-hematological profile characterized by T lymphocyte depletion, and a relative high proportion of auto-immune diseases.

3.5. Angiolipomatosis (ORPHA #199279; OMIM #206550)

3.5.1. Diagnosis

Angiolipomatosis is a rare disease with unknown prevalence, most of the time sporadic, rarely inherited on an autosomal dominant or recessive mode, without identified genes [25]. Angiolipomas usually present as solitary nodules or as multiple subcutaneous nodules, typically on the arms and trunk of men (Fig. 4). They may be painful, sometimes with a dissociation between the lesion and a strong complaint.

3.5.2. Physiopathology and histology

Angiolipomas arise from highly innervated fascia, especially on puberty (hormonal influence) or after repeated traumatisms. They associate intermingled adipocytes and vessels. Microthrombi could lead to painful necrosis of blood vessels and adipocytes leading to inflammation. It is not known if angiolipomatosis is a specific disease, a vascular subtype of FML, or a phenotypic expression of other entities such as Cowden syndrome. Some angiolipomas could be neoplastic due to microdeletion of chromosome 13, a region containing the retinoblastoma gene, a tumor suppressor gene. Pseudoangiomatous spindle cell lipoma is a rare pattern within the spindle cell lipoma spectrum exhibiting a special histological pattern similar to vascular lesions, creating a pseudoangiomatous appearance [26]. Approximately 20 to 30 reports have been described in the literature.

3.5.3. Treatment

Resection of angiolipomas may be complicated with painful recurrent inflammation. Tricyclic antidepressant, which also inhibits serotonin and adrenalin reuptake with antihistaminergic

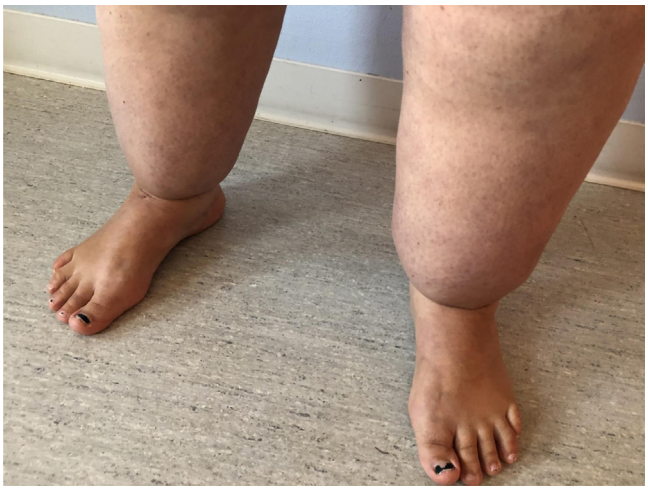

Fig. 5. Leg lipedema.

effects, may control the release of mast cell mediators, with a potential good therapeutic effect.

3.6. Lipedema (OMIM #614103)

3.6.1. Diagnosis

Lipedema, still named *Lipohyperplasia dolorosa*, is a chronic progressive disease characterized by abnormal fat distribution resulting in disproportionate, painful limbs, especially butt, thighs and calves, more rarely hips or upper arms (Fig. 5). It doesn't affect hands or feet. It almost exclusively affects women, generally leading to considerable disability and psychosocial distress. Literature shows both scarce and conflicting data regarding its prevalence. Lipedema is considered a rare entity but may be a more frequent condition than thought.

Features for lipedema have been defined using ultrasound (increased subcutaneous adipose tissue), lymphoscintigraphy (slowing of the lymphatic flow and a frequent asymmetry between the lower extremities), computed tomography (symmetrical bilateral soft tissue enlargement without either skin thickening or subcutaneous edema), MRI (increased subcutaneous adipose tissue), MR lymphangiography (enlarged lymphatic vessels up to a diameter of 2 mm), and dual-energy X-ray absorptiometry (fat mass in the legs adjusted for body mass index (BMI) $\geq$ 0.46 or fat mass in the legs adjusted for total fat mass $\geq$ 0.38) [27].

3.6.2. Physiopathology

Polygenic susceptibility combined with hormonal, microvascular, and lymphatic disorders may be partly responsible for its development, but indeed lipedema pathophysiology remains unknown, and an etiological treatment is not yet available.

3.6.3. Treatment

Weight loss measures exhibit minimal effect on the abnormal body fat distribution, resulting in eating disorders, increased obesity risk, and psychological consequences. Surgical techniques, such as liposuction and excisional lipectomy, represent therapeutic options in selected cases [28,29].

3.7. Hibernomas

3.7.1. Diagnosis

In contrast with previous lipomatosis which are mainly made of white fat cells, hibernomas are uncommon benign neoplasms of brown adipose tissue, coined about the presence of brown fat in hibernating animals [30,31]. Described by Merkel in 1906, these tumors are similar to (and often mistaken with) lipomas or liposarcomas, slow growing, painless, but have unique imaging and histopathologic feature. Hibernomas generally present in young adults with a mean age of 38, in the thigh, shoulder, and back (regions rich in brown adipose tissue). They are often warm to touch owing to their vascularity; otherwise, the physical exam features of these neoplasms are nonspecific.

Commonly used imaging modalities include ultrasonography showing well-defined borders and high-echoic lesions with abundant blood flow signals, computed tomography (CT) demonstrating well-circumscribed, lobulated soft tissue masses, with sometimes internal septations. On T1- and T2-weighted MRI images, hibernomas appear isointense or slightly hyperintense with fat-suppressed sequences showing high signal intensity (Fig. 6), with heterogeneous enhancement patterns. Due to the high metabolic activity and abundance of mitochondria in brown adipomas, they exhibit elevated FDG uptake on PET-CT and may raise issues to differentiate from malignancies [30].

Differential diagnosis with liposarcoma requires histological diagnosis.

3.7.2. Physiopathology and histology

Histopathological features suggest an origin from fetal brown fat tissue, but these tumors rarely occur in infants, and possibly represent an altered differentiation pathway of brown fat. Reciprocal translocations of chromosome 11q have been implicated especially in the regions involving tumor suppressor genes *MEN1* and *AIP*. Also, hibernomas may be associated with multiple endocrine neoplasia type 1. Hibernomas can have variable histopathologic composition depending on their histological subtypes and the amount of brown fat cells resulting in 4 classes 1) typical (> 70% of brown adipocytes), 2) lipoma-like (containing white adipocytes, 3) myxoid, and 4) spindle cell variants. These 2 last less common variants are most often located in the posterior neck and shoulder. The brown fat marker gene *UCP1* a mitochondrial protein transporter, is consistently expressed in hibernoma. Hibernoma may also contain fat cells resembling lipoblasts, which makes it difficult to distinguish it from atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS). Although nuclear expressions of murine double minute 2 (*MDM2*) and cyclin-dependent kinase 4 (*CDK4*) are widely used as immunohistochemical surrogate markers for ALT/WDLS, nuclear expression of *MDM2*, *USP7* and p 53 are also expressed in most hibernoma at difference with *CDK4* [31].

3.7.3. Atypical localization

Some localization are very rare such as breast hibernoma [32] or intraosseous hibernoma [33], most often detected in the spine and pelvis of older adults. Intraosseous hibernomas are generally small, sclerotic, and frequently found incidentally and can raise concern for metastasis. Whether or not these tumors are related to soft tissue hibernomas is uncertain. Finally, an increased potential for hibernomas to arise as spontaneous neoplasms in some animal models such as Sprawgue-Dawley mice has important implications in studies involving peroxisome proliferators-activated receptor (PPAR) drugs, lipophilic environmental chemicals (e.g., polychlorinated biphenyls), and other molecules (e.g., beta-adrenergic stimulation) that may target brown fat adipocytes [34].

3.7.4. Treatment

Most of the time, a surgical resection is proposed.

4. Syndromic lipomatosis

The classification of syndromic lipomatoses initially reported in Proteus, Cloves, or Cowden syndromes, have been deeply modified

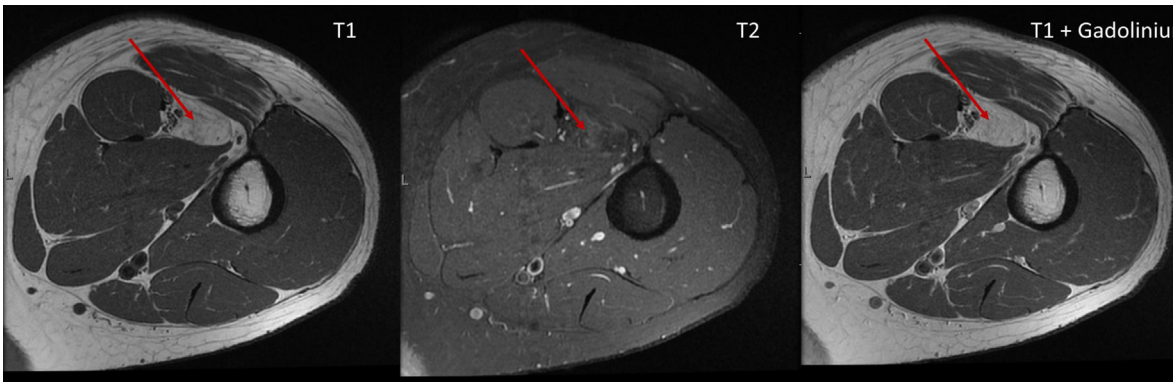

Fig. 6. MRI imaging of a hibernoma located on the right medium gluteal muscle in a MEN1 patient.

with advances in genetic knowledge. As of today, mutations in the *PIK3CA*, *LMNA*, *MEN1* genes, mitochondrial genes such as MERRF, and some rarer genetic pathways have allowed a new genetic classification. Other genetic conditions such as MEN1 or NF1 have been associated with lipomatosis (Table 2B).

4.1. PIK3CA-related disorders (ORPHA #530313)

Currently identified PIK3CA-related disorders presented in Fig. 7 [35] are classified according to the association with 1. an overgrowth syndrome (PROS), 2. vascular, or 3. non-vascular malformations. *PIK3CA*-related PROS disorders include some lipomatoses figuring in Table 2B, and in bold italic in Fig. 7. Mosaic gain-of-function mutation in *PIK3CA* gene leads to abnormal Akt-mTOR pathway activation which results in abnormal tissue growth. Diagnosis is complicated by the variability and overlap in phenotypes associated with *PIK3CA*-related disorders [36–38]. Inhibitors of mTOR such as sirolimus (= rapamycine) have been proposed in treatment, but more recently alpesilib, a PI3Kα-selective inhibitor, has proven its effectiveness and safety in the management of PROS [39]. Phenotypic variants of PROS such as Proteus syndrome, first reported by Cohen and Hayden, had been described before the identification of *PI3KCA* mutations, as a sporadic hamarto-neoplastic syndrome characterized by an asymmetric, disproportionate overgrowth of any connective tissues, such as bone, fat (large subcutaneous or internal lipomas), or epidermal nevi, in a mosaic or patchy pattern [40]. The prevalence is about 1/1,000,000 live births. Proteus syndrome is also caused by mutations in components of the PI3K-AKT signaling cascade, the most common mosaic gene alterations being in *AKT1* gene [41]. AKT1 inhibitor miransertib may be proposed in this setting.

4.2. Cowden syndrome/PTEN (ORPHA #201; OMIM#158350)

4.2.1. Diagnosis

PTEN hamartoma-tumor syndrome (PHTS) is a rare autosomal dominantly inherited condition caused by germline mutations of *PTEN* gene, associated with multiple hamartomatous lesions occurring in various tissues, including the gastrointestinal tract, skin, mucous membranes, breast, thyroid, endometrium, and brain (Table 3) [42]. Lipomas, if ≥ 3, are a minor criteria of diagnosis.

4.2.2. Physiopathology

PTEN (phosphatase and tensin homolog) gene, encodes a phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase protein, containing a tensin-like domain and a tyrosine phosphatase catalytic domain. Unlike most of tyrosine phosphatases, this protein preferentially dephosphorylates phosphoinositide substrates and negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate. It functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway.

4.2.3. Treatment

Early screening of cancers associated to the syndrome is required especially for breast, thyroid, colorectal, endometrial, and renal cancers.

4.3. Familial partial lipodystrophy syndrome

4.3.1. LMNA (ORPHA #280365; OMIM#150330)

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, cardiovascular and gynaecological complications [2–4]. Familial partial lipodystrophy syndrome especially related to mutation R482 of the *LMNA* gene (FPLD2) are characterized by cervico-facial fat distribution and may be associated with small lipomas of the abdominal wall despite the body subcutaneous lipoatrophy [43]. In lipomas, the adipogenic machinery is impaired in lipodystrophic fat coming from lipoatrophic regions, although the histological phenotype is near-normal, exhibiting low-grade inflammatory features [44].

4.3.2. LIPE (ORPHA #435660; OMIM #615980)

Other recessive types of lipodystrophy syndromes such as *LIPE* or *CIDEC* variants may be associated with lipomatosis [45,46]. A phenotype of myopathy and lipodystrophy syndrome (facio-troncular MSL-like lipomatosis with relative lipoatrophy from the lower extremities), has been reported associated with a homozygous Lipase E gene (*LIPE*) mutation [45,46]. *LIPE* gene encodes the hormone sensitive lipase, a key enzyme for triglyceride metabolism, expressed in adipocytes and neurological tissue.

4.3.3. CIDEC

Otherwise, Cidea and Cidec are lipid droplet-associated proteins that promote lipid storage in brown and white adipose tissue. *CIDEC* gene variants could favor familial thigh lipomatosis mimicking the classical "saddlebag" phenotype. *CIDEC* genes participate in the regulation of energy expenditure among lipid droplets, peroxisomes, and mitochondria through the *CIDE-ATGL-PPARα* pathway in adipocytes [47]. Other genes such as Calcyphosine-like (*CAPSL*) have also been involved.

4.3.4. MFN2

Mutations in the *MFN2* nuclear gene coding for mitofusin 2, has been reported in autosomic recessive MSL associated with lipoatrophy of non-lipomatous areas with the same pathogenic

Table 2B
Characteristics of the main syndromic lipomatoses.

Lipomatosis type	Mechanism	Classical presentation	Comorbidities	Treatment
Syndromiic lipomatosis				
PIK3CA-related overgrowth syndrome (PROs disorders) (including Proteus syndrome)	–Mosaic gain-of-function variants of PIK3CA –Activation of Akt-mTOR pathway	Lipomatosis sometimes included in: – CLOVES syndrome (*Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal naevi, Scoliosis)* – Fibroadipose hyperplasie or overgrowth – Hemihyperplasia multiple lipomatosis – Fibroadipose infiltrating lipomatosis – Facial infiltrating lipomatosis – Klippel-Trenaunay syndrome – Lipomatosis of nerve		Inhibitors of: –mTOR (sirolimus = rapamycine) – PI3Kalpha (alpesilib) – AKT1 (miransertib)
Cowden/*PTEN* hamartoma syndrome	– *PTEN* variants, tumor suppressor negatively regulating AKT/PKB – Autosomal dominant	–Lipomas (≥ 3) = minor criteria – Hamartomatous lesion (stomach, skin, breast, thyroid, endometrium, brain. . .)	–Macrocephaly, mucocutaneous lesions, gastrointestinal polyps, autism spectrum disorders, intellectual disability – Neoplasia (thyroid, colorectal, endometrial, renal)	– Early cancer screening
Familial partial lipodystrophy syndrome	Variants of: – *LMNA* (FPLD2) Autosomal dominant – *LIPE* (FPLD6),-*CIDEC* (FPLD5) & MFN2 Autosomic recessive	–FPLD2: cervico-facial fat distribution with body subcutaneous lipoatrophy –FPLD6: facio-troncular MSL-like –FPLD5: familial thigh lipomatosis? FPLD6 & MFN2: sometimes classified as pseudolipomatous because of limbs (FPLD6) or non-lipomatous areas (MFN2) lipoatrophy	– Metabolic syndrome (insulin resistance ++) – Fatty liver disease – Cardiovascular complication (coronary, rhythmic) especially for FPLD2	–Metformin –Gliflozines –GLP1 analogs, -metreleptin if low leptin
Mitochondrial disorders (MERRF, MELAS)	Mitochondrial DNA – *MT-TK:* MERFF, – *MT-TI, UUR:* MELAS	Lipomas: 1.7% Frequent diabetes, deafness	MERRF: myoclonus, epilepsy, ragged-red fibers MELAS: Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, & Stroke-like episodes	
Multiple endocrine neoplasia type 1	*MEN1* gene variants Autosomal dominant	Lipomas, hibernomas and leiomyomas	Primary hyperparathyroidism, Pituitary adenoma Neuroendocrine pancreatic and lung tumors. . .	Surgery of hibernomas
Neurofibromatosis type 1	*NF1* gene variants Autosomal dominant RASopathy	Associated lipomas (6%)	Neurofibroma (skin, CNS, peripheral nerves), Ophthalmic lesions, pheochromocytoma Neoplasia (glioma, peripherical nerves, breast, blood)	–
Wilson disease	*ATP7B* gene variants Copper accumulation Autosomal recessive	Limb & trunk subcutaneous lipoma (25%)	Liver and neurological disorders	–no effect of decoppering
Pai syndrome	Unknown	Midline CNS lipomas, mostly corpus callosum	Polyps (facial, nasal mucosa)	–
Encephalocraniocutaneous lipomatosis (Haberland syndrome)	Postzygotic *FGFR1* variant?	Intraspinal or intracerebral lipomas	Hairless fatty tissue nevus (scalp) Choristomas (eye)	–

Table 2C
characteristics of the main visceral lipomatosis (excluding liver steatosis).

Lipomatose type	Mechanism	Classical presentation	Comorbidities	Treatment
Visceral lipomatosis				
Pancreatic lipomatosis	– Acquired: obesity? alcohol hypercortisolemia, steroids – Genetic *CFTR*, *MODY 8 and 5* *SBDS*)	– Common: obesity and metabolic syndrome – Cystic fibrosis especially with diabetes – Lean C-peptide positive maturity-onset diabetes of the young (MODY 5 and 8) – Shwachman-Diamond syndrome or congenital pancreatic lipomatosis: inherited bone marrow failure syndrome	– Hepatic steatosis – Diabetes with exocrine pancreatic insufficiency Neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities	
Adrenal and abdominal myelolipomas	Unknown	– Unilateral adrenal masse (95%) – More frequent in congenital adrenal hyperplasia (bilateral) – Other abdominal sites	Adrenal hormone excess disorders sometimes associated	Surgery only if symptomatic (rare)
Abdominal lipomatosis	Unknown	Located on any abdominal structure – Fibrofatty mesenteric proliferation – Epiploic appendagitis or omental infarction – Mesenteric panniculitis: asymptomatic 50% – Juxtacaval – Abdominal or pelvic lipomatosis (FML) – Renal sinus lipomatosis	– Crohn diseases in fibrofatty mesenteric proliferation) – 50% of cases: Abdominal pain, bloating/distention, diarrhea, constipation, vomiting, anorexia, weight loss, fever, malaise, and nausea – Differential diagnosis: lymphoma (PET-CT)	Mesenteric panniculitis if symptomatic: – Prednisone – Tamoxifen – Surgery if recurrent bowel obstruction
Mediastinal lipomatosis	– Described in Bardet-Biedl syndrome, a ciliopathy – *BBS1* to *BBS12* gene variants – Autosomic recessive	Bardet-Biedl syndrome – Polydactyly, retinitis pigmentosa, – Central obesity, hypogonadism, – Intellectual disability)	Compressive pelvic renal lipomatosis with renal dysfunction	
Spinal epidural lipomatosis	– Unknown – Overweight – Glucocorticoid treatment?	Obesity	Metabolic syndrome	– Weight loss – Surgery
Cardiac steatosis or *lipomatosis cordis* and epicardial lipomatosis	– Steatosis: fatty myocardium without fibrosis – Epicardial fat thickness > 7 mm (Heart US), therefore called lipomatosis	Epicardial lipomatosis associated with – Obesity – Diabetes, metabolic syndrome – Atherosclerosis – Non-alcoholic liver steatosis	– Coronary artery disease – Stroke – Heart failure – Electrical disorders (atrial fibrillation), via paracrine signaling and direct infiltration	– Weight loss – Treatment of metabolic syndrome – Specific cardiac treatment

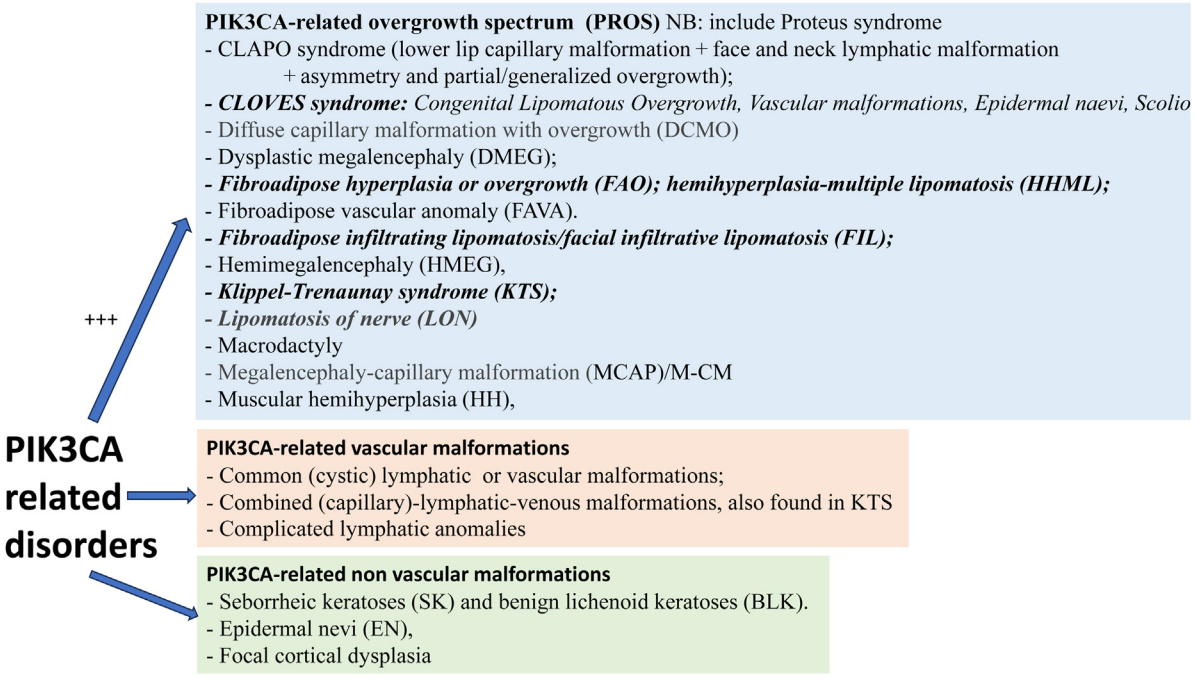

Fig. 7. Classifications of PIK3CA-related disorders.

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 [48]. Involvement of this gene leads to emphasize the role of mitochondria in energy metabolism and to make a link with mitochondrial diseases.

4.4. Mitochondrial diseases.

4.4.1. MERFF *(ORPHA #551; OMIM#545000)*

Lipomas have often been associated with a maternally inherited multisystem mitochondrial disorder especially in patients with mutation in mitochondrial lysine tRNA (mitochondrial thymidine kinase or *MT-TK*) (A8344G mtDNA mutation) which is also the most frequent mutation associated with MERRF (myoclonus epilepsy with ragged-red fibers) [16,49–55]. In the Nation-wide Italian Collaborative Network of Mitochondrial Diseases including1 300 patients, 1.7% (n = 22) of them had lipomas. Among 18% of these 22 patients, MSL was the only clinical manifestation while 54% of patients showed a classical MERRF syndrome. Myopathy, alone or in association with other symptoms, was found in 27% of patients [56].

4.4.2. MELAS *(ORPHA #550; OMIM #540000)*

Besides A8344G mtDNA mutation, other mutations such as 4302 (4302A > G) of the tRNA(Ile) gene (*MTTI*) and 3243 (3243 A > G) of the tRNA(Leu(*UUR*)) causing Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes (MELAS) appear to be a "hot spot" for mtDNA mutations causing chronic progressive external ophthalmoplegia, with diabetes mellitus and multiple lipomas [57,58], while m.8357T > C transition (mitochondrial DNA) has also been involved.

4.4.3. To summarize

The wide phenotypic heterogeneity of mitochondrial diseases should lead to look for variants of mitochondrial genoma, especially in lean C-peptide positive people with diabetes and sometimes maternal inheritance, deafness or non-awaited neuropathic, renal or cardiac complications. MSL is often overlooked by clinicians but could be considered a red flag for mitochondrial disorders, even in patients with an apparently isolated MSL. Life -style intervention may be efficient [59].

4.5. Lipomatosis associated with other genetic conditions.

Multiple Endocrine Neoplasia type 1 (MEN1; ORPHA #652; OMIM#131100) caused by mutations of *MEN1* gene is characterized by a combination of several endocrine (hyperparathyroidism, neuroendocrine pancreatic and lung tumors, pituitary adenoma. . .) and non-endocrine manifestations, among which an increase frequency of neoplasms of the skin (angiofibromas, collagenomas, melanomas), adipose tissue (lipomas and hibernomas (Fig. 6)), and smooth muscle (leiomyomas), with not yet established causality [60–62]. Adrenal liposarcoma may reveal MEN 1 [63].

Neurofibromatosis type 1 (NF1; ORPHA #636; OMIM #162200)-like syndromes (or Legius syndrome) are classified according to the presence of *NF1* and *SPRED1* genes mutations. NF1 is a complex autosomal dominant disorder associated with germline mutations in the *NF1* tumor suppressor gene, belonging to RASopathies, caused by mutations in the Ras/mitogen-activated protein kinase pathway. Despite not mentioned in the French PNDS [64], an Italian review of more than 1000 cases of NF1 found a prevalence of lipomas of 6% besides Café-au-lait macules (96%), axillary and inguinal freckling (90%), neurofibromas (78%), nevus anemicus (3.9%), juvenile xanthogranuloma (3.2%), and melanoma (0.7%) [65,66]. An association between *NF1* gene variants and lipomas with often null phenotype (meaning non-functional allele) has also been reported [66,67].

Wilson disease (ORPHA #905; OMIM#277900) is an autosomal recessive disorder resulting in copper accumulation in the liver and the central nervous tissue. Subcutaneous lipomas were present in 26% of a series of 80 patients with Wilson disease, multiple in 75% of them, mainly found on the extremities and the trunk. Decoppering treatment did not influence the presence or course of lipomas [68].

Pai syndrome (ORPHA #1993; OMIM#155145) was originally described as the presence of a median cleft lip, cutaneous polyps of

Table 3
Diagnosis criteria for Cowden/*PTEN* hamartoma syndrome.

Major criteria	Minor criteria
1 - Breast Cancer	1 - Autism spectrum disorder
2 - Endometrial cancer	2 - Colorectal cancer
3 - Follicular carcinoma of thyroid gland	3 - Esophageal glycogenic acanthosis (≥ 3)
4 - Gastrointestinal hamartomas (including ganglioneuromas, excluding hyperplasic polyps; ≥ 3)	4 - Lipomas (≥ 3)
	5 - Intellectual disability (IQ ≤ 75)
	6 - Renal cell carcinoma
5 - Adult-onset Lhermitte-Duclos disease	7 - Testicular lipomatosis
6 - Macrocephaly (> 97th percentile: 58 cm F & 60 cm M)	8 - Thyroid cancer (papillary carcinoma or follicular variant of papillary carcinoma)
7 - Macular pigmentation of the glans penis	9 - Thyroid lesions (adenoma, goiter. . .)
8 - Multiple mucocutaneous lesions (trichilemmomas, acral keratoses, neuroma, oral papillomas)	10 - Vascular anomalies (venous)

Diagnostic is established if (1) ≥ 3 major criteria including macrocephaly, adult-onset Lhermitte-Duclos disease, or gastrointestinal hamartomas; (2) ≥ 2 major criteria associated with ≥ 3 minor criteria.

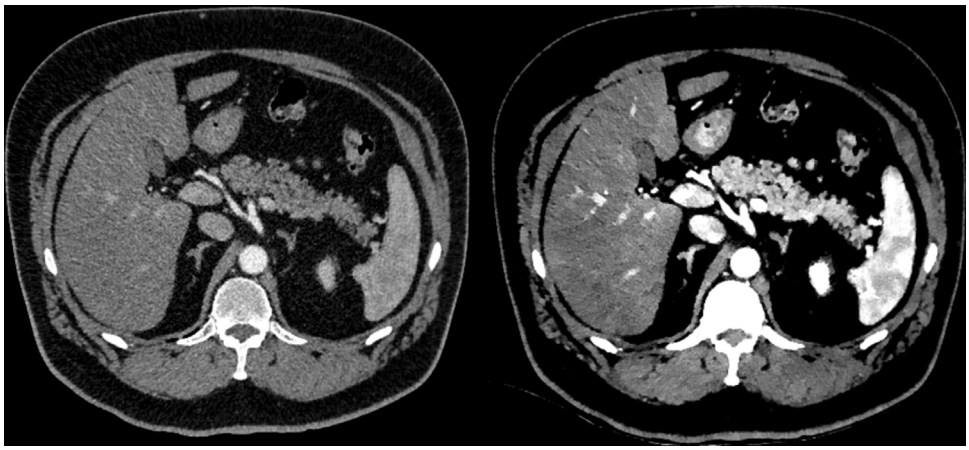

Fig. 8. MRI images of pancreatic steatosis.

the nasal mucosa and face, and midline lipomas of the central nervous system, mostly at the corpus callosum [69]. Exome and/or genome sequencing from blood DNA in 12 patients and from affected tissue in one patient failed to identify any replication in candidate gene, as of today.

Encephalocraniocutaneous lipomatosis (ECCL) or Haberland syndrome (ORPHA #2396; MIM #613001) is a rare congenital neurocutaneous disorder, characterized by unilateral ocular, cutaneous and central nervous system anomalies. Key clinical features include hairless fatty tissue nevus of the scalp, choristoma of the eye and intraspinal and intracerebral lipomas. ECCL is related to postzygotic *FGFR1* mutation and belongs to the Rasopathy group [70].

5. Visceral lipomatosis

Perivisceral depots of fat are sometimes called lipomatosis such as epidural or mesenteric lipomatosis. Nevertheless, lipomas have also been reported as encapsulated tumors in different organs such as adrenals and pancreas (Table 2C). Indeed, fat may be noted in a diffuse or focal manner in a variety of nonneoplastic conditions. The expansion of computed tomography or MRI along with the specific characteristic findings makes the diagnosis of these conditions relatively straightforward. Non-alcoholic liver steatosis will not be considered in this review.

5.1. Pancreatic lipomatosis

Some cases of "pancreatic lipomatosis" may culminate in steatopancreatitis (Fig. 8) and ultimately neoplastic transformations. So far, a fatty pancreas has been related to obesity and ageing, but genetic diseases (cystic fibrosis, Shwachman-Diamond syndrome, and Johanson-Blizzard syndrome), pancreatitis, especially hereditary and obstructive, metabolic and hormonal disorders (hypertriglyceridemia, hypercholesterolemia, hyperinsulinemia and hypercortisolemia), alcohol overuse, drugs such as steroids, diseases of the liver and visceral adiposis may also favor lipomatosis.

5.1.1. Common pancreatic lipomatosis

As regards pancreatic lipomatosis resulting mainly from dyslipidemia and hyperglycemia, is sometimes named "nonalcoholic fatty pancreas disease" [71]. Pancreatic steatosis was also shown to be related to higher visceral fat (VFA), VFA/TFA (total abdominal fat) and hepatic steatosis in a study of living donors of liver, with a cut-off value of VFA ≥ 107 cm^2 predicting pancreatic steatosis [72].

5.1.2. Genetic causes

- Pancreatic lipomatosis is more frequent in subjects with cystic fibrosis-related diabetes (CFRD), as compared to patients without diabetes, and is related to exocrine pancreatic insuffi-

ciency and to severe *CFTR* mutations (classes I to III). Pancreatic calcifications in pancreatic lipomatosis are specific of CFRD [73].

- Chronic pancreatitis with loss of acinar cells, acinar-to-ductal metaplasia, and lipomatosis, with impaired acinar cell regeneration and ductal cell deficiency characterized by shortened primary cilia has also been shown in a mouse model of MODY 5 diabetes, in good correlation with human findings [74].
- Also, CEL-related maturity-onset diabetes of the young (CEL-MODY, MODY8), a type of monogenetic diabetes caused by mutations in the carboxyl-ester lipase (CEL) gene, present with exocrine pancreatic dysfunction (e.g., chronic pancreatitis, pancreas atrophy and lipomatosis) followed by insulin-dependent diabetes, especially in frameshift mutations of exon 11. Hereditary chronic pancreatitis or diabetes may lead to screening for this mutation [75,76].
- Shwachman-Diamond syndrome or congenital pancreatic lipomatosis (ORPHA #811; MIM#260400) is a rare inherited bone marrow failure syndrome characterized by neutropenia, exocrine pancreatic insufficiency, and skeletal abnormalities. In 10–30% of cases, transformation to a myeloid neoplasm occurs. Approximately 90% of patients have biallelic pathogenic variants in the *SBDS* gene located on human chromosome 7q11. Three other genes (*DNAJC21*, *EFL1*, and *SRP54*) have been identified to cause similar phenotypes [77].

5.2. Adrenal (or abdominal) myelolipomas

Adrenal myelolipomas are benign, lipomatous tumors with elements of myeloid cells, most of which present as adrenal incidentalomas and comprise 3.3 to 6.5% of all adrenal masses [78]. Adrenal myelolipomas are usually unilateral (in 95% of cases), variable in size, most often found during midlife, and affect both sexes almost equally. On imaging, adrenal myelolipomas show pathognomonic imaging features consistent with the presence of macroscopic fat. Large adrenal myelolipomas can cause symptoms of mass effect and can occasionally be complicated with hemorrhage. In the event of a concomitant adrenal cortical adenoma or hyperplasia with adrenal myelolipoma, adrenal hormone excess might be detected in patients. Patients with congenital adrenal hyperplasia exhibit a higher prevalence of adrenal myelolipomas than other patient groups and are at risk of developing large and bilateral lesions. Extra-adrenal myelolipoma may occur in different sites: perirenal, in the kidney sinus, presacral, spinal, in the chest, mediastinum, spleen, or pelvis. They are usually asymptomatic; however, in the presence of symptoms, significant growth, or complications, open surgical resection is indicated [78,79].

5.3. Abdominal lipomatosis

In the intestinal tract, the "fat halo sign" usually arises in the context of subacute to chronic bowel wall inflammation. "Fibrofatty mesenteric proliferation" is a characteristic feature of Crohn disease.

In the setting of the acute abdomen, accurate diagnosis of fat-containing lesions (epiploic appendagitis or omental infarction) from other causes of the acute abdomen is critical.

Mesenteric panniculitis is one of the causes of the "misty mesentery", usually corresponding to a benign chronic inflammation and fibrosis of adipose tissue mainly of the small bowel mesentery They are commonly detected incidentally on cross-sectional imaging of the abdomen, are asymptomatic in up to 50% of patients, but may induce abdominal pain, bloating/distention, diarrhea, constipation, vomiting, anorexia, weight loss, fever, malaise, and nausea in the other half. On CT scan, mesenteric panniculitis is seen as a mass-like area of increased fat attenuation, usually located in the left upper quadrant of the abdomen, enveloping mesenteric vessels with frequent lymph node making lymphoma the main differential diagnoses, justifying FDG-PET in some cases. In case of symptoms, prednisone and tamoxifen may be proposed, and surgery reserved in case of recurrent bowel obstruction [80].

Juxtacaval fat deposition is a benign process that has the potential to be confused with more serious conditions.

More diffuse fat deposition (abdominal or pelvic lipomatosis) has the potential to become symptomatic by causing mass effect upon the adjacent structures, for instance in stomach, duodenum, colon. They may also be associated with Familial Multiple Lipomatosis.

Excess fat in the renal sinus may occur with renal sinus lipomatosis or "replacement lipomatosis of the kidney". Fat can also be seen in a variety of postoperative/iatrogenic conditions or abdominal wall/diaphragmatic hernias [81–84].

5.4. Spinal epidural lipomatosis

Spinal epidural lipomatosis is abnormal accumulation of normal fat in the epidural space with weight loss suggested as first-line therapy. It may be favored by glucocorticoid therapy [85,86]. Surgery may also improve quality of life in case of functional consequences.

5.5. Mediastinal lipomatosis

Mediastinal lipomatosis and compressive pelvic renal lipomatosis have been reported in Bardet-Biedl Syndrome a rare autosomal recessive disorder characterized by polydactyly, retinitis pigmentosa, obesity, hypogonadism and mental retardation [87–89].

5.6. Myocardial steatosis

V.6 Myocardial steatosis, also known as *lipomatosis cordis*, is characterized by adipose tissue within the myocardium without significant fibrosis. Besides, *epicardial fat* thickness may be highly protective for the myocardium through brown fat-like thermogenic function, but its thickness strongly correlates with diabetes, atherosclerosis, and coronary artery disease. It is easy to screen with echocardiography and considered abnormal if > 7 mm even if there is not absolute cut-off. It is frequently observed in obesity and non-alcoholic liver steatosis. Besides coronary artery disease, it increases the risk of stroke, heart failure and electrical disorders (atrial fibrillation), via paracrine signaling and direct infiltration [90,91].

5.7. Differential diagnosis

Diagnosis is mainly clinical for isolated and syndromic lipomatosis, or radiological for visceral lipomatosis. An unsightly aspect, pain, functional difficulty, metabolic syndrome are the main circumstances of diagnosis. Different diagnoses need, however, to be ruled out such as common obesity, Cushing's syndrome, especially in MSL, fibromyalgia, lipodystrophy syndromes (which may also be an etiology), lymphoma, neurofibroma, venous malformation, other possible malignant tumors among which atypical lipomatous tumors and liposarcoma [92].

Myxoid liposarcoma, classified in the group of sarcomas with adipose differentiation, is the second most common group of sarcomas. The behavior and clinical course of these tumors can vary widely. A fatty/myxoid component below 50% in MRI are usually high-grade tumors. Also, some well differentiated liposarcoma may present as lipomas [93].

Finally, adult patients with HIV-1 infection on some antiretrovirals, especially thymidine analogue nucleoside reverse transcriptase inhibitors, may present a lipodystrophy syndrome associating peripheral lipoatrophy, central fat accumulation, and

lipomatosis. However, an objective, validated definition of the disorder does not exist, and these patients may also present with MSL, multiple lipomas, isolated buffalo hump or epidural lipomatosis [94].

In addition, acquired partial lipodystrophy syndrome have been reported following bone marrow transplant or total body irradiation during childhood for hemopathy. The pathophysiology is unknown, may be induced by autoimmunity in some cases. [95].

5.8. Physiopathological synthesis

Adipose tissue is known to be highly heterogeneous. This heterogeneity depends on the various anatomical depots which differ according to developmental origin, proliferation ability, glucose and lipid metabolism, insulin sensitivity, hormonal regulation, endocrine secretion, thermogenesis, vascularization, genetic predisposition, environmental factors, gender and age. Individuals with central obesity are more susceptible to developing diabetes and cardiovascular complications, whereas those with peripheral obesity are more metabolically healthy [96].

Besides obesity (most of the time secondary to environmental factors) and lipodystrophy syndromes (most of the time related to genetic or sometimes auto-immune, or iatrogenic causes), lipomatosis is a third group of fat disorder. In this setting, environmental factors, especially excessive alcohol intake, or genetic causes, especially on the Ras-PI3K-PTEN-Akt-mTOR pathway, seem particularly critical.

Alcohol is metabolized in the body via different pathways by the catalytic activity of 3 different enzymes–alcohol dehydrogenase, cytochrome P450 2E1 (CYP2E1), and catalase. Chronic ethanol exposure induces CYP2E1 expression and causes oxidative stress and inflammation of adipose tissue, with alteration of immunity. In addition, lipolysis is increased leading to excess fatty acid release and hepatic steatosis [97,98]. CYP2E1 may also be induced by drugs such as anesthetics, nicotine, dexamethasone, solvents, or other environmental factors. Finally, all causes of chronic adipose tissue inflammation (including associated obesity) may induce alterations of immune balance and increase of serotonin through basophils and mast cells, favoring insulin resistance, obesity, low adipose tissue remodeling, inflammation, and immune alterations.

The Ras-PI3K-PTEN-Akt-mTOR pathway is involved in the regulation of metabolic processes, maintenance of the redox balance, and cell survival and growth. The mTOR pathway, highly conserved during evolution, integrates several environmental cues, such as growth factors, amino acids or glucose, regulates energy metabolism and lipid/protein synthesis, and influences cell survival and growth. Mutations of the *NF1* gene encodes neurofibromin which accelerates the conversion of Ras into an inactive form inducing a deregulation of PI3Kinase-Akt-mTOR pathway [99]. *PTEN* and *MEN 1* genes are tumor suppressor genes, both acting as negative regulator of AKT kinase activity [100]. Their mutations induce proliferation and anti-apoptosis in non-endocrine and endocrine cells.

Finally, genes involved in the function of adipocytes such as those important in nuclear function (*LMNA),* lipid droplets (*CIDEC, LIPE*), or mitochondrial function (*MFN2*, MERFF, MELAS) may also be participate to the occurrence of lipomatoses.

It is not known whether the occurrence of lipomatosis could induce as a consequence a metabolic syndrome. Improving knowledge in the field acknowledge the necessity of registry and networking around adipocyte physiopathology and diseases [101].

6. Conclusion

Lipomatosis are human diseases characterized by the accumulation of benign fat proliferations, associated in the case of Dercum's disease and some angiolipomatosis with a prominent pain complaint, and in some cases but not all (MSL, Dercum, Roch Leri. . .) with a moderate metabolic syndrome. Most of these lipomatoses have been discovered in the 19th century and have since been considered benign. There are currently no specific biological markers, and the differential diagnosis may be difficult especially because of some overlap between the different syndromes. Nevertheless, considerable physio-pathological advances have been made unveiling the role of environmental factors such as alcohol and genetic causes especially affecting pathways involved in energy metabolism (mitochondrial and lipid droplets genes) and those altering the Ras-PI3K-PTEN-Akt-mTOR impairing energy production, cell proliferation and immunity. A better understanding of the underlying pathophysiological mechanisms opens avenues on therapeutic research such as the treatments today available for *PI3KCA*-related disorders.

Authorship statement

All authors participated in the research. Hippolyte Dupuis, Madleen Lemaitre and Marie-Christine Vantyghem performed data analysis and wrote the manuscript. Stéphanie Espiard, Claire Douillard and Arnaud Jannin reviewed the manuscript.

Sources of support

This manuscript was supported by the PHRC 2009_09/094/Clin.gov2009-AO-1169-48.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

Lipodystrophy studies were supported by the French Ministry of Health (Clin.gov2009-AO-1169-48/PHRC-2009_09/094). We are indebted to Geraldine Lavergne and Anne-Sophie Vanceulebroek; the clinical staff of the Department of Endocrinology and Metabolism; the *Délégation à la Recherche Clinique et de l'Innovation* for their support.

Références

[1] Al Ghazal P, Grönemeyer LL, Schön MP. Lipomatoses. J Dtsch Dermatol Ges 2018;16:313–27, http://dx.doi.org/10.1111/ddg.13460.
[2] Zammouri J, Vatier C, Capel E, Auclair M, Storey-London C, Bismuth E, et al. Molecular and cellular bases of lipodystrophy syndromes. Front Endocrinol 2021;12:803189, http://dx.doi.org/10.3389/fendo.2021.803189.
[3] Mosbah H, Donadille B, Vatier C, Janmaat S, Atlan M, Badens C, et al. Dunnigan lipodystrophy syndrome: French National Diagnosis and Care Protocol (PNDS ; Protocole National de Diagnostic et de Soins). Orphanet J Rare Dis 2022;17:170, http://dx.doi.org/10.1186/s13023-022-02308-7.
[4] Vatier C, Christin-Maitre S, Vigouroux C. Role of insulin resistance on fertility - focus on polycystic ovary syndrome. Ann Endocrinol 2022;83:199–202, http://dx.doi.org/10.1016/j.ando.2022.04.004.
[5] Kransdorf MJ, Murphey MD. Imaging of soft tissue tumors. Lippincott Williams & Wilkins; 2006. p. 81. ISBN 978-0-7817-4771-4.
[6] Enzinger and Weiss's soft tissue tumors - NLM Catalog - NCBI. https://www.ncbi.nlm.nih.gov/nlmcatalog/101604149.
[7] Lemaitre M, Chevalier B, Jannin A, Bourry J, Espiard S, Vantyghem MC. Multiple symmetric and multiple familial lipomatosis. Press Med 2021;50:104077, http://dx.doi.org/10.1016/j.lpm.2021.104077.
[8] Lemaitre M, Aubert S, Chevalier B, Jannin A, Bourry J, Prévost G, et al. Rare forms of lipomatosis: Dercum's disease and Roch-Leri mesosomatous lipomatosis. J Clin Med 2021;10:1292, http://dx.doi.org/10.3390/jcm10061292.
[9] Smereczyński A, Kołaczyk K. Is a fatty pancreas a banal lesion? J Ultrasonogr 2016;16:273–80, http://dx.doi.org/10.15557/JoU.2016.0027.
[10] Mick P, Seeberger A, Renkawitz T, Lehner B, Hariri M, Fischer C, et al. Contrast-enhanced ultrasound reveals perfusion differences between benign lipoma and semi-malignant atypical lipomatous tumors: a prospective clinical study. Ultraschall Der Medizin 2023, http://dx.doi.org/10.1055/a-2189-5412.

[11] Pokharel SS, Macura KJ, Kamel IR, Zaheer A, Current MR. imaging lipid detection techniques for diagnosis of lesions in the abdomen and pelvis. Radiographics 2013;33:681–702, http://dx.doi.org/10.1148/rg.333125068.
[12] Holmes LR, Garside JC, Frank J, Livingston E, Snyder J, Abu Khalaf N, et al. In-vivo detection of white adipose tissue browning: a multimodality imaging approach. Sci Rep 2023;13:15485, http://dx.doi.org/10.1038/s41598-023-42537-9.
[13] Kölble K, Veltman G. [Benign symmetrical lipomatosis in women. Association with alcoholic hepatopathy]. Hautarzt Zeitschrift Dermatol Venerologie Verwandte Gebiet 1984;35:33–8.
[14] Lee HW, Kim TH, Cho JW, Ryu BY, Kim HK, Choi CS. Multiple symmetric lipomatosis: Korean experience. Dermatol Surg 2003;29:235–40, http://dx.doi.org/10.1046/j.1524-4725.2003.29056.x.
[15] Borriello M, Lucidi A, Carbone A, Iannone V, Ferrandina G. Malignant transformation of Madelung's disease in a patient with a coincidental diagnosis of breast cancer: a case report. Diagn Pathol 2012;7:116, http://dx.doi.org/10.1186/1746-1596-7-116.
[16] Schoffer K, Grant I. Multiple lipomas, alcoholism, and neuropathy: Madelung's disease or MERRF? Muscle Nerve 2006;33:142–6, http://dx.doi.org/10.1002/mus.20406.
[17] Semenou D, Coeugniet E, Segard M, Martinot-Duquennoy V, Delaporte E. [Launois-Bensaude's disease: report of 17 cases]. Ann Chir Plast Esthet 2008;53:399–407, http://dx.doi.org/10.1016/j.anplas.2007.07.007.
[18] Beek I, van de, Glykofridis IE, Oosterwijk JC, Akker PC, van den, et al. PRDM10 directs FLCN expression in a novel disorder overlapping with Birt-Hogg-Dubé syndrome and familial lipomatosis. Hum Mol Genet 2023;32:1223–35, http://dx.doi.org/10.1093/hmg/ddac288.
[19] Lemaitre M, Chevalier B, Jannin A, Le Mapihan K, Boury S, Lion G, et al. Metabolic and immunological phenotype of rare lipomatoses: Dercum's disease and Roch-Leri mesosomatic lipomatosis. Orphanet J Rare Dis 2021;16:290, http://dx.doi.org/10.1186/s13023-021-01920-3.
[20] 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, http://dx.doi.org/10.1186/1750-1172-7-23.
[21] Siracusa MC, Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, et al. TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation. Nature 2011;477:229–33, http://dx.doi.org/10.1038/nature10329.
[22] Crane JD, Palanivel R, Mottillo EP, Bujak AL, Wang H, Ford RJ, et al. Inhibiting peripheral serotonin synthesis reduces obesity and metabolic dysfunction by promoting brown adipose tissue thermogenesis. Nat Med 2015;21:166–72, http://dx.doi.org/10.1038/nm.3766.
[23] Yabut JM, Desjardins EM, Chan EJ, Day EA, Leroux JM, Wang B, et al. Genetic deletion of mast cell serotonin synthesis prevents the development of obesity and insulin resistance. Nat Commun 2020;11:463, http://dx.doi.org/10.1038/s41467-019-14080-7.
[24] Núñez Ruiz A, Cortés-Garcia JD, Cortez-Espinosa N, Herrera-Rojas PI, Ruíz-Rodríguez VM, Salgado-Bustamante M, et al. Diminished levels of regulatory T cell subsets (CD8+Foxp3, CD4+Foxp3 and CD4+CD39+Foxp3) but increased Foxp3 expression in adipose tissue from overweight subjects. Nutrition 2016;32:943–54, http://dx.doi.org/10.1016/j.nut.2016.02.006.
[25] Garib G, Siegal GP, Andea AA. Autosomal-dominant familial angiolipomatosis. Cutis 2015;95:E26–9.
[26] Shaker N, Blankenship H, Shaker N, Alhalaseh Y, Niu S, Mansoor I, et al. Pseudoangiomatous spindle cell lipoma: a rare and distinct pattern of lipomatous tumors. Int J Surg Pathol 2023, http://dx.doi.org/10.1177/10668969231211337, 10668969231211337.
[27] Parra RFD van la, Deconinck C, Krug B. Diagnostic imaging in lipedema: a systematic review. Obes Rev 2023, http://dx.doi.org/10.1111/obr.13648.
[28] Herbst KL. Subcutaneous adipose tissue diseases: Dercum disease, lipedema, familial multiple lipomatosis, and madelung disease. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc; 2000.
[29] Buso G, Depairon M, Tomson D, Raffoul W, Vettor R, Mazzolai L. Lipedema: a call to action! Obesity 2019;27:1567–76, http://dx.doi.org/10.1002/oby.22597.
[30] Wei R, Chen Z. Hibernomas: a rare benign lipoma subtype. J Surg Case Rep 2023;2023, http://dx.doi.org/10.1093/jscr/rjad472, rjad472.
[31] Tsuda Y, Matsuyama A, Makihara K, Higaki K, Motoi T, Okuma T, et al. Nuclear expression of MDM2 in hibernoma: a potential diagnostic pitfall. Virchows Archiv 2021;478:527–34, http://dx.doi.org/10.1007/s00428-020-02914-5.
[32] Nasner D, Rincón EA, Escobar HF, Sua LF, Mera-Collazos J. Lipoma-like hibernoma of the breast: a case report and literature review. Radiol Case Rep 2023;18:4176–81, http://dx.doi.org/10.1016/j.radcr.2023.08.105.
[33] Gangahar CN, Dehner CA, Wang DP, Amini B, Hillen T, O'Conor C, et al. Intraosseous hibernoma: clinicopathologic and imaging analysis of 18 cases. Histopathology 2023;83:40–8, http://dx.doi.org/10.1111/his.14928.
[34] Bruner RH, Novilla MN, Picut CA, Kirkpatrick JB, O'Neill TP, Scully KL, et al. Spontaneous hibernomas in Sprague-Dawley rats. Toxicol Pathol 2009;37:547–52, http://dx.doi.org/10.1177/0192623309335061.
[35] Canaud G, Hammill AM, Adams D, Vikkula M, Keppler-Noreuil KM. A review of mechanisms of disease across PIK3CA-related disorders with vascular manifestations. Orphanet J Rare Dis 2021;16:306, http://dx.doi.org/10.1186/s13023-021-01929-8.
[36] Kock L de, Cuillerier A, Gillespie M, Couse M, Hartley T, Mears W, et al. Molecular characterization of 13 patients with PIK3CA-related overgrowth spectrum using a targeted deep sequencing approach. Am J Med Genet A 2023, http://dx.doi.org/10.1002/ajmg.a.63466.
[37] Zhang B, He R, Xu Z, Sun Y, Wei L, Li L, et al. Somatic mutation spectrum of a Chinese cohort of pediatrics with vascular malformations. Orphanet J Rare Dis 2023;18:261, http://dx.doi.org/10.1186/s13023-023-02860-w.
[38] Ladraa S, Zerbib L, Bayard C, Fraissenon A, Venot Q, Morin G, et al. PIK3CA gain-of-function mutation in adipose tissue induces metabolic reprogramming with Warburg-like effect and severe endocrine disruption. Sci Adv 2022;8, http://dx.doi.org/10.1126/sciadv.ade7823, eade7823.
[39] Canaud G, Lopez Gutierrez JC, Irvine AD, Vabres P, Hansford JR, Ankrah N, et al. Alpelisib for treatment of patients with PIK3CA-related overgrowth spectrum (PROS). Genet Med 2023;25:100969, http://dx.doi.org/10.1016/j.gim.2023.100969.
[40] Erginel B, Akin M, Yildiz A, Karadag C, Sever N, Tanik C, et al. Proteus syndrome: report of intra-abdominal lipomatosis. Eur J Pediatr Surg Rep 2013;1:38–40, http://dx.doi.org/10.1055/s-0033-1343078.
[41] Schmidt J, Bremmer F, Brockmann K, Kaulfuß S, Wollnik B. Progressive frontal intraosseous lipoma: detection of the mosaic AKT1 variant discloses Proteus syndrome. Clin Genet 2022;102:239–41, http://dx.doi.org/10.1111/cge.14174.
[42] Takayama T, Muguruma N, Igarashi M, Ohsumi S, Oka S, Kakuta F, et al. Clinical Guidelines for Diagnosis and Management of Cowden Syndrome/PTEN Hamartoma Tumor Syndrome in children and adults-secondary publication. J Anus Rect Colon 2023;7:284–300, http://dx.doi.org/10.23922/jarc.2023-028.
[43] Vantyghem MC, Balavoine AS, Douillard C, Defrance F, Dieudonne L, Mouton F, et al. How to diagnose a lipodystrophy syndrome. Ann Endocrinol 2012;73:170–89, http://dx.doi.org/10.1016/j.ando.2012.04.010.
[44] Araújo-Vilar D, Victoria B, González-Méndez B, Barreiro F, Fernández-Rodríguez B, Cereijo R, et al. Histological and molecular features of lipomatous and nonlipomatous adipose tissue in familial partial lipodystrophy caused by LMNA mutations. Clin Endocrinol 2012;76:816–24, http://dx.doi.org/10.1111/j.1365-2265.2011.04208.x.
[45] Sollier C, Capel E, Aguilhon C, Smirnov V, Auclair M, Douillard C, et al. LIPE-related lipodystrophic syndrome: clinical features and disease modeling using adipose stem cells. Eur J Endocrinol 2021;184:155–68, http://dx.doi.org/10.1530/EJE-20-1013.
[46] Zolotov S, Xing C, Mahamid R, Shalata A, Sheikh-Ahmad M, Garg A, et al. Homozygous LIPE mutation in siblings with multiple symmetric lipomatosis, partial lipodystrophy, and myopathy. Am J Med Genet A 2017;173:190–4, http://dx.doi.org/10.1002/ajmg.a.37880.
[47] Zhou L, Yu M, Arshad M, Wang W, Lu Y, Gong J, et al. Coordination among lipid droplets, peroxisomes, and mitochondria regulates energy expenditure through the cIDE-ATGL-PPAR (pathway in adipocytes). Diabetes 2018;67:1935–48, http://dx.doi.org/10.2337/db17-1452.
[48] Capel E, Vatier C, Cervera P, Stojkovic T, Disse E, Cottereau AS, et al. MFN2-associated lipomatosis: clinical spectrum and impact on adipose tissue. J Clin Lipidol 2018;12:1420–35, http://dx.doi.org/10.1016/j.jacl.2018.07.009.
[49] Ripolone M, Zanotti S, Napoli L, Ronchi D, Ciscato P, Comi GP, et al. MERRF Mutation A8344G in a four-generation family without central nervous system involvement: clinical and molecular characterization. J Pers Med 2023;13:147, http://dx.doi.org/10.3390/jpm13010147.
[50] Jeeva-Patel T, Freund P, Margolin EA. Lipomatosis and optic neuropathy clinches the diagnosis of myoclonic epilepsy with ragged red fibres (MERRF) syndrome. BMJ case reports 2021;14:e240463, http://dx.doi.org/10.1136/bcr-2020-240463.
[51] Carré F, Hervochon R, Foirest C, Tankéré F. MERRF syndrome (myoclonic epilepsy with ragged red fibres) presenting with cervicothoracic lipomatosis. Eur Ann Otorhinolaryngol Head Neck Dis 2019;136:113–4, http://dx.doi.org/10.1016/j.anorl.2018.10.015.
[52] Flynn MK, Wee SA, Lane AT. Skin manifestations of mitochondrial DNA syndromes: case report and review. J Am Acad Dermatol 1998;39:819–23, http://dx.doi.org/10.1016/s0190-9622(98)70356-1.
[53] Gámez J, Playán A, Andreu AL, Bruno C, Navarro C, Cervera C, et al. Familial multiple symmetric lipomatosis associated with the A8344G mutation of mitochondrial DNA. Neurology 1998;51:258–60, http://dx.doi.org/10.1212/wnl.51.1.258.
[54] Holme E, Larsson NG, Oldfors A, Tulinius M, Sahlin P, Stenman G. Multiple symmetric lipomas with high levels of mtDNA with the tRNA(Lys) A– > G(8344) mutation as the only manifestation of disease in a carrier of myoclonus epilepsy and ragged-red fibers (MERRF) syndrome. Am J Hum Genet 1993;52:551–6.
[55] Calabresi PA, Silvestri G, DiMauro S, Griggs RC. Ekbom's syndrome: lipomas, ataxia, and neuropathy with MERRF. Muscle Nerve 1994;17:943–5, http://dx.doi.org/10.1002/mus.880170815.
[56] Musumeci O, Barca E, Lamperti C, Servidei S, Comi GP, Moggio M, et al. Lipomatosis incidence and characteristics in an Italian cohort of mitochondrial patients. Front Neurol 2019;10:160, http://dx.doi.org/10.3389/fneur.2019.00160.
[57] Berardo A, Coku J, Kurt B, DiMauro S, Hirano M. A novel mutation in the tRNAIle gene (MTTI) affecting the variable loop in a patient with chronic progressive external ophthalmoplegia (CPEO). Neuromusc Disord 2010;20:204–6, http://dx.doi.org/10.1016/j.nmd.2010.01.006.
[58] Suzuki Y, Suzuki S, Hinokio Y, Chiba M, Atsumi Y, Hosokawa K, et al. Diabetes associated with a novel 3264 mitochondrial tRNA(Leu)(UUR) mutation. Diab Care 1997;20:1138–40, http://dx.doi.org/10.2337/diacare.20.7.1138.

[59] Nadeau E, Mezei MM, Cresswell M, Zhao S, Bosdet T, Sin DD, et al. Self-initiated lifestyle interventions lead to potential insight into an effective, alternative, non-surgical therapy for mitochondrial disease associated multiple symmetric lipomatosis. Mitochondrion 2020;52:183–9, http://dx.doi.org/10.1016/j.mito.2020.03.009.
[60] Al-Salameh A, Cadiot G, Calender A, Goudet P, Chanson P. Clinical aspects of multiple endocrine neoplasia type 1. Nat Rev Endocrinol 2021;17:207–24, http://dx.doi.org/10.1038/s41574-021-00468-3.
[61] Pierotti L, Pardi E, Dinoi E, Piaggi P, Borsari S, Della Valentina S, et al. Cutaneous lesions and other non-endocrine manifestations of multiple endocrine neoplasia type 1 syndrome. Front Endocrinol 2023;14:1191040, http://dx.doi.org/10.3389/fendo.2023.1191040.
[62] Marchand L, Decaussin-Petrucci M, Giraud S, Cotton F, Thivolet C, Simon C. Hibernoma and multiple endocrine neoplasia type 1 syndrome: a non-fortuitous association? A case report and literature review. Ann Endocrinol 2017;78:194–7, http://dx.doi.org/10.1016/j.ando.2017.03.001.
[63] Duro T, Gonzales KL. Adrenal liposarcoma: a novel presentation of multiple endocrine neoplasia type 1. AACE Clin Case Rep 2023;9:10–2, http://dx.doi.org/10.1016/j.aace.2022.11.003.
[64] Neurofibromatose 1. Haute Autorité de Santé. https://www.has-sante.fr/jcms/p_3283954/fr/neurofibromatose-1.
[65] Miraglia E, Moliterni E, Iacovino C, Roberti V, Laghi A, Moramarco A, et al. Cutaneous manifestations in neurofibromatosis type 1. Clin Terap 2020;171:e371–7, http://dx.doi.org/10.7417/CT.2020.2242.
[66] Kluwe L, Friedrich RE, Farschtschi SC, Hagel C, Kehrer-Sawatzki H, Mautner VF. Null phenotype of neurofibromatosis type 1 in a carrier of a heterozygous atypical NF1 deletion due to mosaicism. Hum Mut 2020;41:1226–31, http://dx.doi.org/10.1002/humu.24022.
[67] Ramirez E, Morris SM, Turner TN, Gutmann DH. Familial lipomas without classic neurofibromatosis-1 caused by a missense germline NF1 mutation. Neurol Genet 2021;7:e582, http://dx.doi.org/10.1212/NXG.0000000000000582.
[68] Schaefer M, Gotthardt DN, Didion C, Stremmel W, Weiss KH. Increased prevalence of subcutaneous lipomas in patients with wilson disease. J Clin Gastroenterol 2015;49:e61–3, http://dx.doi.org/10.1097/MCG.0000000000000248.
[69] Lehalle D, Bruel AL, Vitobello A, Denommé-Pichon AS, Duffourd Y, Assoum M, et al. Toward clinical and molecular dissection of frontonasal dysplasia with facial skin polyps: From Pai syndrome to differential diagnosis through a series of 27 patients. Am J Med Genet A 2022;188:2036–47, http://dx.doi.org/10.1002/ajmg.a.62739.
[70] Cattin J, Formet J, Sartelet H, Lenoir M, Riethmuller D, Collardeau-Frachon S. Expending the phenotypic spectrum of encephalocraniocutaneous lipomatosis: about a prenatal case with complete autopsy. Pediatr Dev Pathol 2022;25:180–5.
[71] Kani KK, Moshiri M, Bhargava P, Kolokythas O. Extrahepatic, non-neoplastic, fat-containing lesions of the abdominopelvic cavity: spectrum of lesions, significance, and typical appearance on multidetector computed tomography. Curr Probl Diagn Radiol 2012;41:56–72, http://dx.doi.org/10.1067/j.cpradiol.2011.07.005.
[72] Gursoy Coruh A, Uzun C, Akkaya Z, Halil Elhan A. The relation of CT quantified pancreatic fat index with visceral adiposity and hepatic steatosis. Turk J Surg 2020;36:241–8, http://dx.doi.org/10.47717/turkjsurg.2020.4877.
[73] Alexandre-Heymann L, Puerto M, Martin C, Burnet E, Mosnier-Pudar H, Burgel PR, et al. CT imaging shows specific pancreatic abnormalities in persons with cystic fibrosis related diabetes. Sci Rep 2023;13:10433, http://dx.doi.org/10.1038/s41598-023-37492-4.
[74] Quilichini E, Fabre M, Nord C, Dirami T, Le Marec A, Cereghini S, et al. Insights into the etiology and physiopathology of MODY5/HNF1B pancreatic phenotype with a mouse model of the human disease. J Pathol 2021;254:31–45, http://dx.doi.org/10.1002/path.5629.
[75] Sun S, Gong S, Li M, Wang X, Wang F, Cai X, et al. Clinical and genetic characteristics of CEL-MODY (MODY8): a literature review and screening in Chinese individuals diagnosed with early-onset type 2 diabetes. Endocrine 2023, http://dx.doi.org/10.1007/s12020-023-03512-6.
[76] El Jellas K, Dušátková P, Haldorsen IS, Molnes J, Tjora E, Johansson BB, et al. Two new mutations in the CEL gene causing diabetes and hereditary pancreatitis: how to correctly identify MODY8 cases. J Clin Endocrinol Metab 2022;107:e1455–66, http://dx.doi.org/10.1210/clinem/dgab864.
[77] Kawashima N, Oyarbide U, Cipolli M, Bezzerri V, Corey SJ. Shwachman-Diamond syndromes: clinical, genetic, and biochemical insights from the rare variants. Haematologica 2023;108:2594–605, http://dx.doi.org/10.3324/haematol.2023.282949.
[78] Calissendorff J, Juhlin CC, Sundin A, Bancos I, Falhammar H. Adrenal myelolipomas. Lancet Diab Endocrinol 2021;9:767–75, http://dx.doi.org/10.1016/S2213-8587(21)00178-9.
[79] Duarte Regalado CS, Guzmán Mejía JI, Gutiérrez Uvalle GE, Vargas Rodríguez AE, González Ledo J. A case report and literature review of adrenal myelolipoma. Cureus 2023;15:e43240, http://dx.doi.org/10.7759/cureus.43240.
[80] Sulbaran M, Chen FK, Farraye FA, Hashash JG. A clinical review of mesenteric panniculitis. Gastroenterol Hepatol (N Y) 2023;19:211–8.
[81] Kumar S, Harisankar AG, Singh R, Kumar A, Kumar B, Mandal M. Lipoma of the gastrointestinal tract: a tertiary care centre experience. Ann R Coll Surg Engl 2023, http://dx.doi.org/10.1308/rcsann.2023.0063.
[82] Djuric-Stefanovic A, Ebrahimi K, Sisevic J, Saranovic D. Gastroduodenal lipomatosis in familial multiple lipomatosis. Med Princ Pract 2017;26:189–91, http://dx.doi.org/10.1159/000454714.
[83] Arabadzhieva E, Yonkov A, Bonev S, Bulanov D, Taneva I, Ivanova V, et al. A rare combination between familial multiple lipomatosis and extragastrointestinal stromal tumor. Int J Surg Case Rep 2015;14:117–20, http://dx.doi.org/10.1016/j.ijscr.2015.07.027.
[84] Nureta TH, Shale WT, Belete TD. Giant retroperitoneal well differentiated liposarcoma: a case report and literature review. Int J Surg Case Rep 2023;110:108679, http://dx.doi.org/10.1016/j.ijscr.2023.108679.
[85] Rigsby RK, Barnes S, Sabaté J, Oyoyo U, Chowdhury S, Peters EM. Correlation of spinal epidural fat volume with body mass index: a longitudinal study. Clin Imag 2023;98:61–6, http://dx.doi.org/10.1016/j.clinimag.2023.03.015.
[86] Alnabwani D, Ganta N, Babayev R, Patel V, Shah V, Cheriyath P. Chronic steroid use causing spinal epidural lipomatosis. Cureus 2022;14:e21945, http://dx.doi.org/10.7759/cureus.21945.
[87] Paschou E, Sabanis N. Mediastinal lipomatosis in a patient with Bardet-Biedl syndrome: more diverse than previously thought. Pan Afr Med J 2023;45:82, http://dx.doi.org/10.11604/pamj.2023.45.82.35582.
[88] Kummari M, Narahari NK, Kapoor A, Avala RC, Paramjyothi GK. A rare case of giant mediastino-pleural lipoma. Asian Cardiovasc Thorac Ann 2023;31:739–42, http://dx.doi.org/10.1177/02184923231197694.
[89] Indraneel KS, Rajalakshmi V, Dayanandan Y, Reddy NM. A case of Laurence Moon Bardet Biedl syndrome. J Assoc Phys India 2023;71:1.
[90] Tuzzolo A, Febres-Aldana CA, Poppiti R. Severe myocardial steatosis: incidental finding or a significant anatomic substrate for sudden cardiac arrest? Am J Forens Med Pathol 2020;41:42–7, http://dx.doi.org/10.1097/PAF.0000000000000531.
[91] Iacobellis G. Epicardial adipose tissue in contemporary cardiology. Nat Rev Cardiol 2022;19:593–606, http://dx.doi.org/10.1038/s41569-022-00679-9.
[92] Nishio J, Nakayama S, Chijiiwa Y, Aoki M. Biology and management of deep-seated atypical lipomatous tumor of the extremities. Anticancer Res 2023;43:4295–301, http://dx.doi.org/10.21873/anticanres.16624.
[93] Encinas Tobajas VM, Almeida González C, Marcilla D, Vallejo M, Cano Rodríguez A, Reina Sánchez de Movellán JI, et al. Myxoid liposarcoma: MRI features with histological correlation. Radiologia 2021, http://dx.doi.org/10.1016/j.rx.2021.01.005. S0033-8338(21)00052-7.
[94] Carr A, Emery S, Law M, Puls R, Lundgren JD, Powderly WG, et al. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. Lancet 2003;361:726–35, http://dx.doi.org/10.1016/s0140-6736(03)12656-6.
[95] Ceccarini G, Ferrari F, Santini F. Acquired partial lipodystrophy after bone marrow transplant during childhood: a novel syndrome to be added to the disease classification list. J Endocrinol Invest 2017;40:1273–4, http://dx.doi.org/10.1007/s40618-017-0731-x.
[96] Bäckdahl J, Franzén L, Massier L, Li Q, Jalkanen J, Gao H, et al. Spatial mapping reveals human adipocyte subpopulations with distinct sensitivities to insulin. Cell Metab 2021;33:1869–82.e6, http://dx.doi.org/10.1016/j.cmet.2021.07.018.
[97] Kema VH, Mojerla NR, Khan I, Mandal P. Effect of alcohol on adipose tissue: a review on ethanol mediated adipose tissue injury. Adipocyte 2015;4:225–31, http://dx.doi.org/10.1080/21623945.2015.1017170.
[98] Chiang CH, Lin YH, Kao YC, Weng SC, Chen CM, Liou YM. Mechanistic study of the Aldo-keto reductase family 1 member A1 in regulating mesenchymal stem cell fate decision toward adipogenesis and osteogenesis. Life Sci 2023:122336, http://dx.doi.org/10.1016/j.lfs.2023.122336.
[99] Chevalier B, Dupuis H, Jannin A, Lemaitre M, Do Cao C, Cardot-Bauters C, et al. Phakomatoses and endocrine gland tumors: noteworthy and (not so) rare associations. Front Endocrinol (Lausanne) 2021;12:678869, http://dx.doi.org/10.3389/fendo.2021.678869.
[100] Wang Y, Ozawa A, Zaman S, Prasad NB, Chandrasekharappa SC, Agarwal SK, et al. The tumor suppressor protein menin inhibits AKT activation by regulating its cellular localization. Cancer Res 2011;71:371–82, http://dx.doi.org/10.1158/0008-5472.CAN-10-3221.
[101] Mosbah H, Akinci B, Araújo-Vilar D, Carrion Tudela J, Ceccarini G, Collas P, et al. Proceedings of the annual meeting of the European Consortium of Lipodystrophies (ECLip) Cambridge, UK, 7–8 April 2022. Annal Endocrinol 2022;83:461–8, http://dx.doi.org/10.1016/j.ando.2022.07.674.