Case Report

Madelung Disease-a Challenge in Clinical Practice

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Abstract

Multiple Symmetric Lipomatosis (MSL) or Madelung's disease is a rare disorder of the lipid metabolism characterized by symmetric growth of sometimes massive unencapsulated fatty deposits (lipomas) in anatomical regions ranging from typical sites such as neck, occipital area, upper arms, face, abdomen and back to the more unusual involvement of the scrotum and the tongue. In this article we present the diagnostic and therapeutic challenges in a patient developing an acute oligoarticular attack of gout generating important functional incapacity, alcoholic liver disease potentially evolving to liver cirrhosis, heart and kidney failure, bilateral parotid gland region swelling and Madelung disease. The recognition and screening for potential complications related to the Madelung disease is of great practical importance because treatment priorities should be stratified accordingly.

Keywords: Gout; lipomatosis; Lipoma; Madelung disease; Multiple symmetric

1 Introduction

Multiple Symmetric Lipomatosis (MSL) or Made lung's disease is a rare disorder of the lipid metabolism characterized by symmetric growth of sometimes massive unencapsulated fatty deposits (lipomas) in anatomical regions ranging from typical sites such as

neck, occipital area, upper arms, face, abdomen and back to the more unusual involvement of the scrotum and the tongue [1, 2]. The epidemiology of the disease is linked to middle aged male patients of mostly of European Mediterranean origin. The etiology of the disease is still unknown, but possible causes point to mitochondrial DNA (mtDNA) mutations, abnormal adipose tissue and the patient's positive history of chronic alcohol abuse [1, 3]. The consequences of the fatty accumulations are usually cosmetic, but dyspnea, dysphagia and difficulty in head movement have also been described in cases where lipomas of the neck region were more severe. An MSL classification has been proposed: Type 1 - involving symmetric, well circumscribed fat masses in the neck, proximal upper limbs and superior thorax; Type 2 - involving diffusely distributed subcutaneous fat layers with the appearance of simple obesity and Type 3 - fat deposits mainly located in the pelvic region resembling a gynecoid appearance [4, 5].

2 Case Report

A 77-year-old male patient presented with a history of bilateral knee and wrist joint pain, prolonged morning stiffness and walking incapacity, chronic lumbar pain, episodic constrictive chest pain correlated with moderate physical effort, fatigue and weight loss of 5 kg in the last 6 months. He identified himself as a nonsmoker but admitted a continuous moderate daily alcohol intake in the last 15 years. He denied experiencing xerophthalmia, xerostomia or dysphagia. On admission, clinical examination revealed a BMI of 30.6 kg/m^2, facial venectasias and dyspnea on exertion. Painless bilateral and symmetric soft tissue tumors were present in the preauricular and nuchal region. Similar soft tissue tumors were identified at the levels of the chest and of the superior abdominal wall (Figure 1). Further physical examination revealed a respiratory frequency of 18/min, O_2 saturation of 95%, persistent atrial fibrillation, NYHA stage III heart failure, arterial hypertension stage IIc, bilateral coarse crackles in the lower pulmonary lobes, swollen knees and wrists, both with limited flexion and extension movements, walking incapacity both due to the bilateral knee involvement and intermittent claudication (stage IIa Leriche Fontaine). Complementary lower limbs and heart ultrasound (US) evaluation identified lower extremity arterial disease and a low left ventricular ejection fraction <40%. US evaluation of the visible soft tissue tumors in the neck, upper limbs and trunk regions revealed the presence of unencapsulated lipomas with fibrous septa. No Doppler signal was detectable.

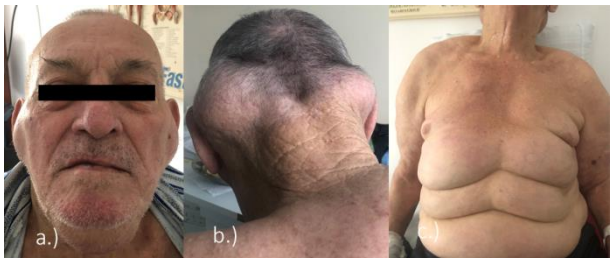

Figure 1abc: Bilateral, symmetric soft tissue masses in the preauricular and nuchal region, upper arms, chest and upper

abdominal wall.

Complete blood count (CBC) and biochemistry was performed. The lab analyses identified the presence of mildly elevated CRP (0.8mg/dl), uric acid (8.7 mg/dl) and MEV (103.8 fL), no anemia, and decreased platelet number (131x103/µL) as well as creatinine clearance (71.38 ml/min). The rest of the CBC and biochemistry analysis were normal. Antinuclear antibodies panel, viral markers for B and C hepatitis were negative. The prostate-specific antigen, albumin, cholesterol and triglycerides were all in normal range. Musculoskeletal US evaluation of the hands identified mild bilateral radiocarpal synovitis and proximal as well as distal interphalangeal joint osteophytes. At knee level, bilateral joint effusion with crystal aggregates was identified, the double contour sign (highly specific for uric deposition) was present at the level of the hyaline femoral cartilage and hyperechoic cloudy aggregates were detected at the level of the patellar tendon bilaterally (Figure 2). Synovial fluid analysis identified the presence of needle-shaped intracellular and extracellular crystals, characteristic for monosodium urate crystals.

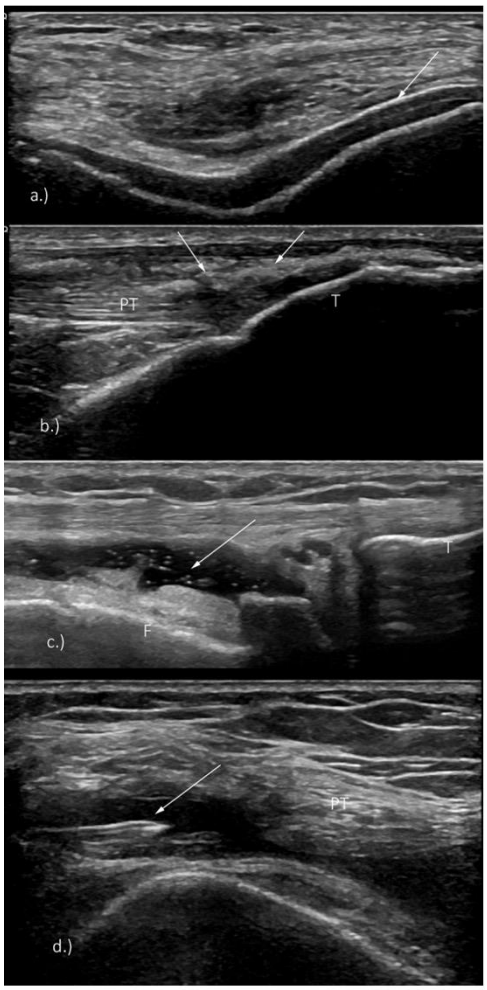

Figure 2a: Double contour sign at the level of the hyaline femoral cartilage; **b)** Arrows -Hyperechoic cloudy aggregates were detected at the level of the patellar tendon (PT) bilaterally, T – tibia cortical bone; **c)** Lateral parapatellar recess distended by a hypoechoic mass (arrow) containing hyperechoic dots, F – femoral bony cortex, T – tibia bony cortex; **d)** Transverse scanning of the suprapatellar bursa and ultrasound guided aspiration of the knee effusion (arrow – tip of the needle, PT – patellar tendon). The salivary glands US evaluation showed a normal volume and echotexture of the parotid, submandibular and sublingual glands. In the proximity of the superior pole of both parotid glands, unencapsulated subcutaneous fat tissue masses were detected (Figure 3).

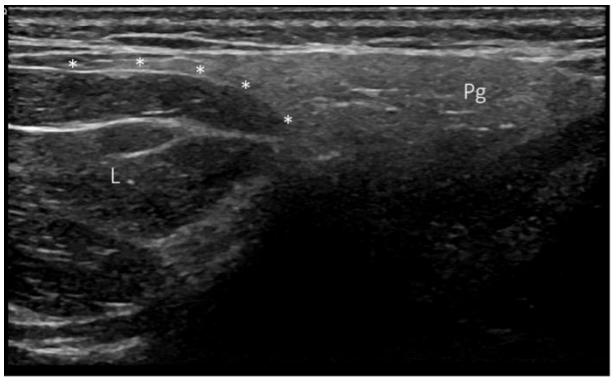

Figure 3: Normal Parotid Gland (Pg) and the unencapsulated subcutaneous fat tissue mass localized adjacent to the superior parotid pole (L).*- showing the interface between the fatty mass and parotid gland.

Apart from a diffuse intima thickening of the carotid arteries, no jugular or thyroid gland abnormalities were present at US evaluation. Thoraco-abdominal CT was performed in order to assess potential compressive intrathoracic and intraabdominal lipomatous masses or underlying neoplasias. In our patient, CT evaluation was negative for both. In addition, hepato-splenomegaly was detected. A more complex liver status evaluation was initiated in the gastroenterology department, given also the positive history of chronic alcohol consumption. Dual Energy X-ray Absorptiometry (DEXA) examination confirmed the diagnosis of vertebral and hip osteoporosis.

According to our evaluation, the patient's diagnoses were the following: uric microcrystal arthropathy affecting both articular and periarticular structures, alcoholic liver disease potentially evolving to liver cirrhosis, heart and kidney failure and Madelung disease. The first phase treatment strategy was US guided corticosteroid knee joint injection with immediate recovery of the walking capacity, colchicine and allopurinol prescription for the long-term uric acid level control. The first step in the treatment approach had a major positive functional outcome and was possible without any additional risk due to prior exclusion of life threatening MSL complications (e.g. obstructive respiratory disorder caused by a combination

of lipoma compression and/or pharyngeal adipose tissue infiltration). In addition, anticoagulants, digoxin, diuretics, betablockers and statins were prescribed for optimizing the cardiovascular and renal parameters and controlling the associated risk factors. Furthermore, the patient was transferred to the gastroenterology department for supplementary investigations.

2.1 Discussion and review of the literature

Herein we present the diagnostic and therapeutic challenges in a patient presenting with an acute attack of gout in the knees generating walking incapacity, alcoholic liver disease, bilateral parotid gland region swelling and Madelung disease. The recognition and screening for potential complications related to the Madelung disease is of great practical importance because treatment priorities should be stratified accordingly.

2.2 Epidemiology and classification

As of 2007, more than 300 cases of MSL have been reported worldwide, with a more consistent prevalence in Mediterranean countries such as Italy, Spain and France, but reports of patients range as far as far as southeast Asia [6-8]. Patients are usually male (male to female ratio 15:1) with a prior history of alcohol abuse [9]. Three main subgroups of MSL with distinct clinical appearances upon physical examination have been proposed, although interpolated physical aspects of the subtypes can occur. MSL Type 1 involves symmetric, well circumscribed fat masses in the neck, nuchal area of the head, shoulders, proximal part of the upper limbs and superior thorax, giving the appearance of a „Michelin Man“; MSL Type 2 presents as diffusely distributed subcutaneous fat layers that are mostly unelevated and extend on a greater surface of the body, resembling simple obesity; MSL type 3 was introduced at a later date and characterizes the gynecoid distribution of the fatty tissue in the pelvic region and gynecomastia [4, 5]. The presence of the lipomas in the neck region can resemble a collar-Madelung's collar-a symmetrical structure with rather cosmetic consequences for the patient.

2.3 Etiology

Several theories have been postulated regarding the genesis of MSL. One of the particular findings in Madelung adipose tissue is the presence of brown fat. Brown fat is responsible for thermogenesis in babies without the involvement of chills. It becomes increasingly atrophic with age, to the point where only remnants are identifiable in healthy adults. The thermogenesis is physiologically mediated through the following mechanism: β3 receptors found in brown fat are highly responsive upon stimulation via Norepinephrine (NA), increasing the intracellular concentrations of Adenylate Cyclase (AC) via Gs proteins. Uncoupling protein 1 (UCP-1) uncouples the AC induced downhill cascade of Adenosine Triphosphate (ATP) production, favoring heat production instead [10, 11]. It is currently believed that a functionally defective brown fat tissue is present in MSL lipomas. NA responsiveness is decreased in MSL brown adipose tissue and NA fails to generate effective levels of Inducible Nitric Oxide Synthase (iNOS), responsible for anti-proliferative effects. The decreased adrenergic innervation of Madelung adipose tissue causes increased local storage of triglycerides, changes in the local lipid metabolism and hyperplasia of the adipose tissue [12, 13]. It should be noted that not all Madelung lipomas present brown fat components, so other possible mechanism of the disease should also be considered

[14]. A secondary effect is that of alcohol, which not only decreases β receptor levels, further perturbing the adrenergic system, but also has a direct adipogenic effect. Several studies have linked the pathogenesis of the disease to mutations in mitochondrial DNA (mtDNA) (m.8344A>G and m.8363G>A). According to one study, up to 16% of the patients presented mtDNA mutations [15]. The m.8344A>G mutation is also present in MERRF syndrome, pointing to a possible common ground of the two disease entities [16, 17]. These mutations have been inconsistently reported in other studies and cases of MSL with wild type status of the mtDNA in MSL adipocytes have also been reported [14, 18].

2.4 Morphology and functionality of the adipocytes

Probe excision biopsies from patients with MSL have not only shown differences in the architecture of the fatty tissue but also in the individual cells. Compared to normal adipose tissue, the Madelung adipose tissue presents smaller adipocytes, more prominent septa and more atypical nuclei [18]. Further studies have identified the resemblance of the Madelung adipose tissue to that of the brown fat, through the presence of brown adipocyte markers such as UCP-1. It should be noted that UCP-1 and the brown fat associated with it is not present in all subjects and that it decreases with patient age and grade of obesity [14]. The growth kinetic of the Madelung adipocytes has shown changes in in vitro studies. Compared to normal adipocytes, these cells have demonstrated a higher growth potential, reaching a steady phase at higher cell concentrations. Interestingly, the secretome of the Madelung adipocytes can influence the phenotype of normal adjacent adipocytes and induce a switch towards an aberrant phenotype, thus decreasing the population doubling time and modifying the surface markers in previous healthy adipocytes. This points to an invasive character of the disease that also influences adjacent healthy tissue regions [18]. Surface phenotype of the Madelung adipocytes differs from the normal adipocytes' one through reduced levels of CD90, CD9, CD73 and CD49f and increased levels of CD49a. This could lead to differences in adipogenic differentiation (CD90), proliferation and ATP metabolism (CD73). Lower CD9 levels are also linked to poorer cell adhesion and increased protection from cellular senescence [18, 19].

2.5 Diagnosis and clinical presentation

Diagnosis is usually established through physical examination. The hallmark of the disease is the presence of multiple sometimes symmetrical lipomas of sizes ranging from 1 to 20 cm in different body regions. Although the lipomas are easily spotted by physicians in regions with reduced physiological adipose tissue such as the nuchal area or the neck region, MSL type 2 or type 3 could be easily misinterpreted as simple obesity or gynecomastia [9, 20]. Patient history and temporal succession of events described by the patient are key in assessing the correct diagnosis. MSL usually has an abrupt progression at disease onset, afterwards becoming stationary for long periods of time and is correlated with chronic alcohol abuse and weight gain without apparent changes in patient diet [21, 22]. Disease progression is usually deemed slow and painless, patients usually complaining about difficulty upon actions requiring neck movement. Compression of adjacent neck structures, such as the carotid arteries and jugular veins, cervical plexus, recurrent laryngeal nerves, trachea and esophagus and infiltration further down into the mediastinum can lead to more severe symptoms of dysphagia, dyspnea, dysphonia, venous

stasis and paresthesias. Several case reports have also highlighted the involvement of the tongue in MSL, depicting macroglossia as an additional property of the disease [23, 24]. Other more unusual particularities of this disease are the involvement of the scrotum or of the facial nerve with consequent paresthesias and paresis in the face region [1, 25]. Other disease clusters, such as hyperuricemia, hypertriglyceridemia, hypercholesterolemia, macrocytic anemia or different stages of hepatopathy that might be present are usually linked to chronic ethanol abuse and are not necessarily a consequence of the primary Madelung disease itself [21, 26].

The presence of polyneuropathy is currently believed to be of mixed genesis, both due to chronic alcohol toxicity and direct effects of the disease itself. CT and MRI are both excellent imaging techniques in helping establish the severity of lipoma infiltrations and possible compression of adjacent structures. CT and MRI examinations should be used in order to establish the possible presence and extent of mediastinal or abdominal lipomas that are inaccessible to US examination and as a preoperative management tool in symptomatic cases of MSL. US evaluation is useful in diagnosing superficial adipose masses, such as those in the face or neck region. US is a quick diagnostic method, efficient in time sensitive circumstances such as ambulatory patient presentation but lacks the accuracy of CT and MRI in diagnosing deeper located lipomas and their infiltration [27, 28].

2.6 Differential diagnosis

The pseudoathletic appearance of type 1 MSL could sometimes resemble cushingoid syndromes, whereas type 2 MSL is typically misdiagnosed as simple obesity [29].The presence of gynecomastia and/or gynecoid adipose tissue distribution requires further exclusion of alternative etiologies such as estrogen excess of tumoral or nontumoral cause, decreased testosterone or androgen resistance (primary causes - Klinefelter syndrome, secondary causes - Kallmann syndrome), decreased testosterone concentrations via systemic diseases (end stage renal disease, thyrotoxicosis, liver cirrhosis), drugs (spironolactone, efavirenz, ethanol, busulfan, vincristine, ketoconazole) [30]. The presence of lipomas in the neck region requires exclusion of other benign or malignant regional masses: cervical lymphadenopathy (reactive or malignant), goiter, carotid artery aneurysms, oropharyngeal squamous cell carcinoma, neurofibromas, salivary gland (infiltrations, neoplasms, cysts), congenital disorders such as thyroglossal duct cysts, and branchial cleft anomalies. Multiple lipomas and lipid dystrophies are also consequences of HAART therapy in HIV positive patients. These modifications are attributed to the effect of protease inhibitors [31-34]. In our case, salivary gland and neck region US examination performed immediately at bedside was extremely helpful for an accurate local evaluation and immediate exclusion of several differential diagnoses.

2.7 Associations with alcohol intake and other metabolic disorders

Alcohol consumption has been established to worsen the symptoms of MSL. The vast majority of the case reports published in the literature include patients with a positive history of alcohol abuse. The cessation of alcohol consumption does indeed slow the growth of lipomas but does not reduce the size of the already developed adipose masses [35]. The presence of MSL in patients denying alcohol consumption or even children speaks against alcohol as a solitary cause of the disease.

Alcohol should rather be categorized as a catalyzer in the development of the lipomas. Other complications of chronic alcohol abuse in patients with MSL include liver disease, hyperuricemia, alcoholic pancreatitis and macrocytic anemia [36]. Polyneuropathy is present in several cases described in the literature. Axonal predominant neuropathy as well as autonomic dysfunctions are also common neurological complications of chronic alcohol consumption, so alcohol should be regarded as a cofactor in the disease pathogenesis. Evidence pleading for a mixed pathogenesis is the presence of neuropathy in children suffering from MSL and adults denying prior alcohol abuse. Histological features of MSL neuropathy also differ from those of ethanol induced neuropathy (progressive axonal atrophy in MSL vs. wallerian degeneration of the axon and reduced myelination), [37-39]. Other case reports have highlighted the presence of osteoporosis in patients suffering from MSL. The presence of osteoporosis in a male patient requires the exclusion of a possible Cushing syndrome resembling MSL or other osteolytic etiologies (glucocorticoid medication, hypogonadism, hyperparathyroidism, excessive alcohol consumption, gastrointestinal disease) [40].

3 Complications

Although not very frequent, if complications of MSL are present, they are usually linked to difficulties in neck movement and compression of adjacent neck or mediastinal structures. The most significantly impacted structures are the larger blood vessels (carotid arteries, brachyocephalic and jugular veins), nerves (cervical plexus, recurrent laryngeal nerves, facial nerve, glossopharyngeal nerve), trachea and the main bronchi, esophagus, regional lymph nodes and the thoracic duct. Rare cases of scrotal lipomatosis associated with dysuria and painful erections have also been reported [25]. The main concern is the presence of dyspnea, stridor or sleep apnea, all pointing to a significant obstructive respiratory disorder caused by a combination of lipoma compression, pharyngeal adipose tissue infiltration and macroglossia [41]. Very few cases of malignant transformation to liposarcoma or intramyxoid sarcoma have been described in the literature [42, 43].

4 Treatment

Nonsurgical treatments, such as intralipotherapy using phosphatidylcholine/ deoxycholate, only prevent further growth of the pathological adipose tissue, without reducing the actual volume. Eliminating alcohol consumption may also prevent further disease progression. Injection of enoxaparin and β2 agonists (salbutamol) has proven inconsistent curative effects [44, 45]. Surgical removal of lipomas is currently the main choice of treatment. The preferred methods are either through lipectomy or liposuction. Lipectomy allows for a better exposure of the desired adipose mass, while providing the surgeon with a superior view of adjacent structures., but the unencapsulated nature of the lipomas significantly impacts full excision capabilities. Being a more invasive procedure in comparison to liposuction, far more procedural complications have been reported [6, 45]. Liposuction is less invasive, but procedural success is significantly hindered if the adipose mass presents an important fibrous component. US assisted liposuction may be useful in differentiating tumor limits from critical structures, especially in the neck. The two surgical options are considered palliative. Recurrence is almost certain, due to incomplete lipoma resection through both methods [45, 46]. In patients presenting advanced stages of

obstructive pulmonary disease, and MSL associated sleep apnea, CPAP is deemed the main conservative therapy [47, 48]. If proven unsuccessful, more invasive choices of either transoral or transcervical lipectomy or pharyngoplasty should be considered [49]. An idealistic approach in treating MSL would require the fulfillment of the following criteria: fully removing the already existent lipomas from the patient's body, thus improving the cosmetic appearance, lowering the risk of developing severe complications (obstructive pulmonary disease, compression of vascular and nervous structures), and guaranteeing a very low risk of recurrence.

5 Conclusion

In our patient, we have dealt with a classical Type 1 Madelung disease. US evaluation on admission allowed for a rapid exclusion of parotid gland involvement and of other possible lymphadenopathies of the head and of the neck. CT scan of the thorax was essential in excluding possible life-threatening compressive phenomena in the neck, thorax (thoracic wall and mediastinum) and abdomen. Due to the lack of complications other than the modified cosmetic appearance, the patient did not opt for elective surgical excision of the lipomas. Nonsurgical therapy was also not a valid choice, due to the stationary status of the lipoma volume in the last years. The patient was encouraged to immediately cease alcohol consumption.

Conflict of interests

The authors declare none.

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