Multidisciplinary diagnostic dilemma in differentiating Madelung’s disease — the value of superb microvascular imaging technique: A case report

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BACKGROUND
Madelung’s disease, also known as multiple symmetrical lipomatosis, is a rare, underrecognized disorder of fat metabolism that results in unusual accumulation of subcutaneous fat deposits around the neck, shoulders, upper arms, trunk, hips, and upper thighs. Our case demonstrates the importance of differential diagnosis and the value of a superb microvascular imaging technique for suspecting and confirming Madelung’s disease. Timely diagnosis and alcohol abstinence could prevent the progression of growing fatty masses and prevent surgery.

CASE SUMMARY
A 62-year-old male was admitted to the Rheumatology center complaining of symmetric subcutaneous tumors in the area of the parotid and submandibular salivary glands, small soft masses in the occiput and upper third of the forearm, rashes on calves. A high titer of rheumatoid factor and low concentrations of serum complements were detected. The high-end ultrasound and magnetic resonance imaging examinations of all affected areas of the soft tissues showed predominantly adipose tissue (lipomas) without suspicion of liposarcoma. The
INTRODUCTION

Madelung’s disease (rare disease code ORPHA:2398) is also known as familial benign symmetrical lipomatosis, multiple symmetric lipomatosis (MSL), cephalothoracic lipodystrophy, or Launois-Bensaude syndrome[1]. It is characterized by symmetrical accumulation of fatty tissue, usually around the head and neck, the trunk, upper arms, and other less common places according to the type of disease. Patients with a history of chronic alcoholism comprise 60%-90% of cases and suffer from secondary liver cirrhosis[2,3]. Mediterranean men from 30-year-old to 60-year-old appear to be at highest risk[1,4]. The exact prevalence and incidence are unknown, but estimates are available for certain countries (e.g., the prevalence for males in Italy is 1/25,000)[1,2]. A vast complex of life-threatening disorders often occurs with Madelung’s disease including liver cirrhosis, diabetes, dyslipidemia, hyperuricemia, gynecomastia, neuropathy, hypothyroidism, chronic obstructive pulmonary disease, and adrenal dysfunction[1,5].

There are no specific tests for diagnosing this disorder, and the diagnosis is mostly based on history, clinical appearance, and the results of imaging examinations. Due to the slow growth of fat masses and alcohol-influenced decreased self-care, the disease is often recognized late. The changes in a patient’s facial appearance due to fat accumulation are often mistaken with the widely known chronic alcoholism-induced pseudo-Cushing syndrome (also known as “facies alcoholica”)[6]. Early diagnosis and alcohol cessation might prevent the progression of growing fatty masses and avoid surgery.

We report a case of a patient diagnosed with liver cirrhosis and progressive symmetrical fat accumulation, showing difficult differential diagnosis and the value of high-end ultrasound imaging for making an accurate diagnosis.
CASE PRESENTATION

Chief complaints
A 62-year-old male was admitted to the Vilnius University Hospital Santaros Clinics Rheumatology department presenting with growing symmetric subcutaneous tumors in the area of the parotid and submandibular salivary glands, small soft masses in the occiput, and the upper third of the forearm. The patient also complained about bilateral small hand joint pain and morning stiffness for 6 mo, dryness of the mouth, rash on calves, and nail deformations for several years.

History of present illness
The subcutaneous tumors in the area of the parotid and submandibular salivary glands were present for 2 years and grew more rapidly in the last 7 mo. The patient had a history of moderate alcohol consumption (mostly beer) and was diagnosed with metabolic liver cirrhosis (Child-Turcotte-Pugh [CTP] B class; Model for the End-Stage Liver Disease [MELD] score equal to 9), portal hypertension (splenomegaly, hypersplenism, paraumbilical shunt), and secondary megaloblastic anemia in 2019. Since then, he was followed up by a gastroenterologist. In 2019, the ultrasound examination of the neck and salivary glands’ soft tissues discovered only small, lush adipose tissue around the neck without enlarged lymph nodes. At first, facial changes were associated with phenotypical changes due to alcohol-induced hypercortisolism. However, the masses continued to grow, the patient was referred for a rheumatologist’s consult. In September 2020, the patient consulted with the rheumatologist and was hospitalized in the Rheumatology department for further diagnosis.

History of past illness
The patient was previously diagnosed with primary arterial hypertension and polyneuropathy, effectively treated with alpha-lipoic acid. No oncological history was reported. Past exposure to chemical substances of unknown origin in a working environment at a fertilizer factory was noted.

Personal and family history
The patient had a history of moderate alcohol consumption, but he abstained from consuming alcohol for approximately > 6 mo. He claimed to have no other hazardous habits, and no allergies to food or medicines. There was no history of surgical treatment and congenital or similar disorders in his family.

Physical examination
During the examination, egg-sized hard and painless subcutaneous tumors in the area of the parotid and submandibular salivary glands, soft and small masses in the occiput, hump, the upper third of the forearm. Occipital and neck area masses were difficult to notice without a meticulous inspection. Minor gynecomastia (elastic masses, which could be moved without causing the patient any pain and had no definite margins) was suspected. The palpation of the small joints of both hand was painful. Onychodystrophy, rashes on calves — red patches of skin covered with thick, silvery scales, and dry tongue were observed. The patient was a bit overweight (body mass index 25.5 kg/m²).

Laboratory examinations
Changes in the blood test results showed elevated erythrocyte sedimentation rate (ESR) by 26 mm/h, a high titer of rheumatoid factor (RF) 235.0 U/mL, low levels of complement C4, normal immunoglobulin (Ig) G 1.26 g/L, and a normal cyclic citrullinated peptide antibody test. Extractable nuclear antigen antibodies and anti-neutrophil cytoplasmic antibodies were negative. Schirmer’s test was positive (right eye: 6 mm/5 min, left eye: 5 mm/5 min). Laboratory test results were also compatible with the diagnosis of alcohol-related liver cirrhosis (aspartate aminotransferase > 2× alanine aminotransferase, slightly elevated γ-glutamyl transferase, mild coagulopathy, and megaloblastic anemia). Calculated alcoholic liver disease/nonalcoholic fatty liver disease index was 14.2, meaning 100% probability of alcohol-related liver disease. Viral hepatitis markers were negative. Hyperglycemia and hyperuricemia were also noted (Table 1).

Imaging examinations
Ultrasound examination of the soft tissues of the parotid glands and neck area showed...
Table 1 Main laboratory findings

| Main laboratory findings                        | Value | Normal range          |
|-----------------------------------------------|-------|-----------------------|
| Hemoglobin (g/L)                              | 109   | 128-160               |
| MCV (fl)                                      | 102   | 78-96                 |
| MCH (pg)                                      | 34.1  | 26-31                 |
| Platelet count (1/L)                          | 70    | 130-400 × 10^9        |
| C reactive protein (mg/L)                     | 4.22  | < 5                   |
| Erythrocyte sedimentation rate (mm/h)         | 26    | ≤ 10                  |
| Glucose (mmol/L)                              | 6.70  | 4.2-6.1               |
| Aspartate aminotransferase (U/L)              | 57    | < 40                  |
| Alanine aminotransferase (U/L)                | 22    | < 40                  |
| γ-glutamyl transferase (U/L)                   | 123   | ≤ 36                  |
| Alkaline phosphatase (U/L)                    | 181   | 40-150                |
| Total bilirubin (mol)                         | 17.5  | < 21                  |
| Albumin (g/L)                                 | 37    | 36-52                 |
| SPA (%)                                       | 62    | 70-130                |
| Creatinine (µmol/L)                           | 68    | 62-110                |
| Uric acid (µmol/L)                            | 510   | 208-428               |
| INR by Owren                                   | 1.24  | 0.90-1.19             |
| Complement C4 (g/L)                           | 0.14  | 0.15-0.57             |
| Complement C3c (g/L)                          | 0.7   | 0.9-1.8               |

INR: International normalized ratio; MCH: Mean corpuscular hemoglobin; MCV: Mean corpuscular volume; SPA: Stago prothrombin assay.

Figure 1 Photos of the patient showing multiple tumorous masses. A: Profile view: symmetrical, firm, and non-tender fatty masses in the area of parotid salivary glands (upper arrow); soft and highly mobile submandibular mass (lower arrow); B: Side view: occipital and neck area masses (arrows); C: Frontal view: submandibular, parotid masses and gynecomastia (arrows).

Figure 2 shows high-resolution ultrasound images (using Canon Apio i800 14 MHz linear probe with power Doppler [PD] and color superb microvascular imaging [SMI] techniques) of the fatty tumor close to the left parotid gland area. Grayscale ultrasound showed typical superficial lipoma well-circumscribed with parallel linear and thin echogenic lines (Figure 2A). Features that suggest
malignancy include: the presence of thick septa (> 2 mm), the presence of nodular and/or globular or non-adipose mass-like areas, and decreased percentage of fat composition (< 75% fat)[7]. Lipomatous soft tissue lesions with only thin septa that do not enhance at magnetic resonance imaging (MRI) can be confidently confirmed as a lipoma[8]. PD detected several small internal dots — more than minimal flow/vasculality (Figure 2B). Liposarcoma is characterized mostly by an ill-defined and usually vascularized margin, heterogeneous texture[9], SMI confirmed several unrelated vascular dots, which caused only weak suspicion of liposarcoma (Figure 2C). The random noise during the examination was minimized. Ultrasound examination of the breasts displayed mild bilateral gynecomastia: left 22 mm × 6 mm and right 28 mm × 7 mm. Head and neck MRI showed the significantly thickened subcutaneous fat layer at the damaged areas and confirmed ultrasound diagnosis — it is more likely lipomatosis than liposarcoma (Figure 3A and B).

**Further diagnostic work-up**

Other possible comorbidities were excluded: Spirometry for chronic pulmonary disease and electroneuromyography for polyneuropathy were without changes. A small salivary gland biopsy was performed and showed no histological signs of Sjogren’s syndrome or amyloid deposition.
Psoriasis was confirmed by a dermatologist, and high-resolution ultrasound imaging (using Canon Aplio i800 24 MHz linear probe) showed active synovial arthritis in the metacarpophalangeal joints (Figure 4A-C).

**FINAL DIAGNOSIS**

Benign symmetrical lipomatosis (Madelung’s disease), type I, metabolic liver cirrhosis (CTP B, MELD 9), megaloblastic anemia, toxic peripheral polyneuropathy, hyperuricemia, gynecomastia along with psoriasis and moderate activity psoriatic arthritis (DAS28 — 4.94 points), were diagnosed.

**TREATMENT**

The patient was informed about the importance of alcohol abstinence and weight control. The symptomatic treatment for comorbidities was recommended: hepatoprotection for cirrhosis, alpha-lipoic acid for previously diagnosed polyneuropathy, allopurinol for hyperuricemia, small doses of methylprednisolone 6 mg per day for psoriatic arthritis.

**OUTCOME AND FOLLOW-UP**

Although the patient did not consume alcohol for > 6 mo, and his liver enzymes normalized, he noticed that fatty masses continued to grow. He felt tremendous and socially isolating cosmetic discomfort due to the changed physical appearance around the neck. Therefore, he was referred to a maxillofacial surgeon for surgical treatment, and a lipectomy was performed. A histological examination of the removed tissue confirmed the diagnosis of benign symmetrical lipomatosis.

The patient was referred to an endocrinologist due to hyperglycemia. We also recommended getting an appointment with a dietologist to manage the diet. As the patient doesn’t have dyslipidemia yet, prevention and a healthy lifestyle must be the priority. The gastroenterologist should also observe the patient every 3-6 mo due to cirrhosis and its complications. The follow-up visit to the rheumatologist was set after a month. Repeated check-ups and ultrasound imaging are needed to observe possible disease regression and evaluate the progression of other fatty masses.
DISCUSSION

MSL is a very rare lipid metabolism disorder described by the localization of fat masses in different combinations of distribution. Donhauser et al[10] classified it into three types: first type — dominant cervical localization, second — pseudo athletic appearance, third — changes are located mostly in the abdomen area (Figure 5). The pathogenesis of the disease is unclear. It is thought that the disease might develop as a result of defects in mitochondrial function of adipose tissues, decreases in cytochrome C oxidase activity, and catecholamine-induced fat deposition. Alcohol consumption influences a decreased number and activity of β-adrenergic receptors and promotes fat synthesis[11]. It can also directly affect mitochondrial activity and cause premature oxidation of mitochondrial DNAs or mitochondrial DNA mutation, resulting in fat accumulation throughout the body[12]. Systemic diseases, such as primary hypothyroidism, Cushing’s syndrome, giant cell anemia, diabetes, epilepsy, and malignant diseases, may also be associated with the development of Madelung’s disease[11,13].

Precise physical examination of the whole body is essential for suspected symmetrical lipomas as patients usually complain only about the most obvious discomforting masses, while other affected areas are missed. In our case, the patient had dominant masses in the head and neck area. Gynecomastia in men with MSL is very rare, and in most cases, is not a presenting symptom[14]. Other masses of fat were not so expressed visually.
The differential diagnosis of systemic rheumatic diseases, such as Sjogren’s syndrome and IgG4-related disease, was performed due to salivary glands’ masses, elevated ESR and RF, low complements, positive Shirmer’s test, and arthritis. According to the classification criteria, Sjogren’s syndrome was excluded: immunological and histopathological tests were negative\cite{15}. Common features of IgG4 syndrome, like IgG4-related autoimmune pancreatitis, swelling of or within an organ system (an inflammatory pseudotumor), salivary gland disease (material from salivary glands didn’t show lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells and fibrosis), lymphadenopathy, skin manifestations (only psoriasis was confirmed), and symptoms consistent with allergies or asthma were not detected. Also, serum IgG4 concentration was not elevated\cite{16}.

Ultrasound imaging is usually the first step in the investigation, differentiation, and confirmation of lipomas. SMI is an innovative ultrasound Doppler technique that provides visualization of low velocity and microvascular flow never seen before with the ultrasound\cite{17}. SMI can suppress noise caused by motion artifacts with an intelligent filter system without eliminating the weak signal arising from small vessel blood flow and using any contrast agent. Hence it achieves a greater sensitivity than the conventional PD technique. There are two modes: color (cSMI, which demonstrates B-mode and color information simultaneously) and monochrome (SMI, which focuses only on the vasculature)\cite{18}. Both modes demonstrate the value in differentiating a wide variety of clinical situations: benign and malign tumors (density and shape of tumor vessels), the therapeutic effect of the treatment (chemotherapy or immunosuppressive treatment), inflammatory diseases (synovial vascularity in arthritis, colitis) many other medical conditions\cite{19,20}. The main disadvantage is that there are no studies and standards on the application of SMI for liposarcoma. The main tips for evaluation lipomatous tissue are comparing SMI and PD images with focusing on mSMI mode, which is more sensitive for vasculature, adjusting gain, and other settings.

In this case, SMI was used for better visualization of vascularity in differentiating lipomas and arthritis. If pathological vascularity and heterogeneous echotexture are suspected, then MRI is preferred over computed tomography for excluding liposarcoma. Malignant degeneration of fatty tissue into liposarcoma has only been reported in two MSL cases\cite{21,22}. Also, ultrasound tools help to confirm even a small accumulation of adipose tissue in the most common areas according to the type of disease when it is not visually expressed. Confirmed symmetrical lipomatosis helps to differentiate Madelung’s disease, and ultrasound is the most useful tool for determining the disease type.

Comorbidities, such as dyslipidemia, hypertension, chronic obstructive pulmonary disease, hypothyroidism, and diabetes mellitus, often co-occur with Madelung’s disease\cite{1,13}. Diseases related to alcohol abuse, such as chronic liver disease, macrocytic anemia, and peripheral neuropathy, are also common in MSL patients. In our case, the patient was firstly diagnosed with metabolic liver cirrhosis and was continuously followed up by a gastroenterologist. His facial appearance due to adipose tissue accumulation was assumed to be alcohol-related, although he was not a heavy drinker. Additionally, clinically significant neuropathy was also diagnosed, which is also highly relevant to alcohol abuse. Also, several new metabolic disorders were
diagnosed: hyperglycemia and hyperuricemia. Although our patient stopped alcohol consumption and cirrhosis was under control, fatty masses continued to grow (while it is expected that alcohol withdrawal stops Madelung’s disease progression). Active psoriatic arthritis (DAS28 — 4.94 points) could have been a trigger of the fatty masses’ growth after alcohol abstinence.

Madelung’s disease is difficult to diagnose at the early stages, as patients mostly seek medical help due to obvious cosmetic disorders or when liver cirrhosis and other comorbidities have already been developed. The main challenge for the doctors is to combine all the co-occurring symptoms into one disorder. In our case, predominant masses looked like solid tumors in the area of parotid glands imitating Sjogren’s syndrome and IgG4-related disease (Mikulicz disease). Ultrasound confirmed that tumors in the parotid glands area were not related to salivary glands and were closely located in front of them.

The primary treatment of Madelung’s disease is symptomatic. Alcohol withdrawal and weight loss are essential to control MSL. However, it does not guarantee the inhibition or reversion of the disease[5,23]. There is no effective pharmacotherapy in treating Madelung’s disease to date[5]. Lipectomy or liposuction is the only available effective treatment[23,24]. However, there is no consensus on the optimal surgical approach, and the overall recurrence rate is up to 63%[23,25]. Despite the high recurrence rate, the surgical approach must be considered as MSL also affects social life and worsens overall quality of life[26]. The histological investigation of the surgical material is essential, as there is always a small risk of liposarcoma. If the patient refuses surgery, ultrasound imaging control is strongly recommended, especially in cases of rapid mass growth.

Patients with Madelung’s disease need long-term observation and multidisciplinary systemic management of comorbidities[27]. It is also important to observe these patients due to disease relapse, the need for re-operation, and possible liposarcoma by ultrasonography. There are no established intervals for the patient’s surveillance.

CONCLUSION

Ultrasoundography has an important role in differentiating fatty tumors, particularly when evaluating tissue homogeneity and vascularity. Nevertheless, high-end ultrasound imaging value for confirming the diagnosis and/or follow-up for malignancy is unquestionable. However, wider and further large scale investigations are needed to standardize this technique. The further evaluation of active psoriatic arthritis as a trigger of fatty mass growth is also a question of interest. Increasing awareness of the presence of Madelung’s disease could prevent misdiagnosis and misleading care management. Due to its variety of manifestations, it still remains a multidisciplinary diagnostic dilemma.

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