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Review
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MADELUNG'S DISEASE: CASE REPORT AND REVIEW OF THE LITERATURE

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SUMMARY

Madelung's disease is an extremely rare disorder of unknown etiology, characterized by prominent, symmetric masses of adipose tissue on the neck, shoulders, arms and upper parts of the trunk. Although benign in its nature, tongue or mediastinal involvement can cause compression syndromes of the trachea and superior vena cava leading to dyspnea, dysphagia and dysphonia. It predominantly affects men between the ages of 30 and 60 years, of Mediterranean origin and with a history of alcohol abuse. The disorder can also be associated with hyperlipoproteinemia, hyperuricemia, diabetes mellitus and hypothyroidism. The only effective treatment is surgical removal or liposuction, but recurrences are common. A case of a 51-year-old man with unusual pseudoathletic appearance, history of excessive alcohol consumption and subcutaneous fat tissue biopsy is presented and typical features of Madelung's disease are discussed.

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INTRODUCTION

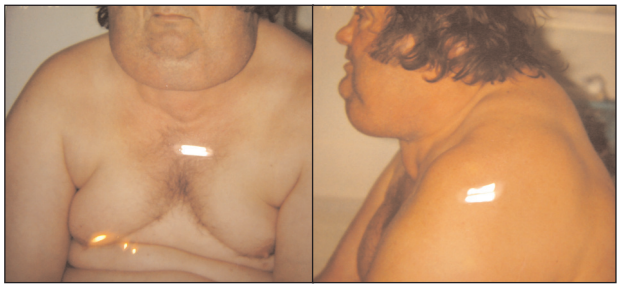
Benign symmetric lipomatosis (BSL) or Madelung's disease is a rare condition characterized by massive symmetric deposits of non-encapsulated adipose tissue in the upper trunk, neck and head (1,2). It affects more often males aged 30-60 years, and is more common among residents of Mediterranean European countries. The condition develops over a period of months to years. Patients usually complain of their cosmetic appearance, although the enlargement of fat deposits in advanced cases can cause dyspnea or dysphagia (3). Besides strong association with chronic alcoholism, frequently associated findings include diabetes mellitus, lipid disorders, liver disease and hypothyroidism, but the exact cause has not yet been identified (2,3).

We report on a case of a 51-year-old man with a history of alcoholism who reported masses in his cervicofacial, nuchal and upper arm regions that had gradually enlarged over a period of 2 years.

CASE REPORT

A 51-year-old man was admitted to our hospital for bilateral swelling in his upper arms, cervicofacial and nuchal region, which had started two years before and had progressively enlarged (Fig. 1). He denied any

Figure 1. **Photograph of the patient showing dorsal lipomas over cervical and upper thoracic spine, and large lipomas in the submandibular and anterior neck region.**



dyspnea or dysphagia, drug use, or other medical conditions. His medical history was significant for his occasionally excessive alcohol intake. Physical examination revealed a well-developed man, in good clinical condition. On admission, his height was 174 cm, weight 91 kg, and body mass index (BMI) 30 kg/m^2. The chest and abdomen physical examination was unremarkable and neurological examination was negative. Blood pressure was 120/80 mm Hg, pulse rate 68/minute. Bilateral swelling of the submandibular, cervical, nuchal, upper back regious and upper arms was present, freely movable, painless and non-tender. Subcutaneous masses varied in size to maximum circumference of about 10 cm. No lymphadenopathy was found.

All laboratory and endocrinological data were within the normal limits except for elevated gamma glutamyltransferase (GGT) (Tables 1 and 2). Exercise testing and ECHO were within the normal range. Computed tomography (CT) scan showed extensive fatty accumulation in the cervical and upper thoracic region with no mediastinal involvement or blood vessel dislocation (Fig. 2).

Subcutaneous fat tissue biopsy obtained from the dorsal upper thoracic region showed normal fat tissue without malignant changes. A definitive diagnosis of Madelung's disease was made on the basis of the patient's medical history of alcoholism, increased fatty tissue accumulation and histological examination. Surgical treatment was indicated to remove tumor masses.

Figure 2. **Computed tomography showing subcutaneous fatty masses in the anterior neck and occipital region**

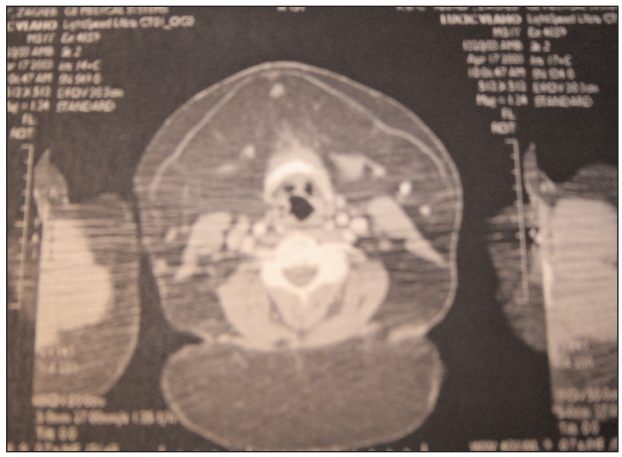


Table 1. **Laboratory data**

Total cholesterol	5.08 mmol/L
HDL-cholesterol	1.41 mmol/L
LDL-cholesterol	3.17 mmol/L
Triglycerides	1.11 mmol/L
WBC	5800/mL
RBC	5060x10^3/mL
Hb	15.9 g/dL
MCV	88 fl
ESR	5 mm/h
Glucose	5.2 mmol/L
Insulin	3.8 mU/L
Creatinine	98 μmol/L
K	4.4 mmol/L
Na	140 mmol/L
YGT	103 U/L
AF	88 U/L
AST	36 U/L
ALT	44 U/L

Oral glucose tolerance test (OGTT)		
Time	0 min	120 min
Glucose	3.8 mmol/L	4.9 mmol/L

Table 2. **Endocrinological data**

ACTH	349.4 pg/mL
Cortisol	28.9 μg/mL
GH	2.4 mU/L
TSH	1.8 mU/L
fT4	11.1 pmol/L
Anti-thyroid antibody	Negative
LH	8.2 U/L
FSH	4.7 U/L
Testosterone	28.9 nmol/L
Estradiol	0.18 nmol/L
Prolactin	12.9 μg/L
Progesterone	1.5 nmol/L
DHEA-SO4	1.1 μmol/L
Androstenedione	1.6 nmol/L

DISCUSSION

Madelung's disease is an uncommon, hereditary disorder defined as the presence of multiple and symmetric fatty accumulations, usually involving the upper trunk, neck and head. Although it predominantly affects middle-aged men of Mediterranean origin and with a history of alcohol abuse, a few cases have also been reported in children (2,3). The disorder can be defined as a "sight diagnosis" disease because of the typical pattern of distribution of the masses that do not recede even with a reduced calorie intake. Massive symmetric deposition of fat becomes cosmetically deforming in the parotid region ("hamster cheeks"), cervical region ("horse collar"), and posterior neck ("buffalo humps") (3).

Madelung's disease was initially described by Sir Benjamin Brodie in 1846 (4). In 1888, Otto Madelung reported the first series of 33 patients with lipomas associated with alcoholism, and in the next year Launois and Bansaude presented a total of 65 patients with similar features (5,6). Since then, about 200 patients have been reported in the literature. Besides Madelung's disease, several descriptive names have been attributed to this condition, including benign symmetric lipomatosis, multiple symmetric lipomatosis, lipomatosis simplex indolens, and symmetric adenolipomatosis (3).

Our patient came from the Mediterranean region of Croatia, but his family history of a similar disorder was negative. His phenotype was close to type 1 clinical phenotype of Madelung's disease, which includes male sex, and fat accumulation in the neck, shoulders, upper arms and upper back. Type II clinical phenotype is present in both sexes and characterized by a superabundant female fat distribution in the upper back, deltoid region, upper arms, hips and upper thigh region (7).

Although the disorder is benign, rarely tongue or mediastinal involvement occurs, resulting in compression syndromes of the trachea and superior vena cava, which can cause dyspnea, dysphagia and dysphonia (8-10). These symptoms were not present in our patient. Histological analysis revealed typical, non-encapsulated fat tissue, with extension into the surrounding structures, characterized by normal-sized or smaller than expected adipocytes with spindle cell proliferation, suggesting active, localized recruitment and differentiation of preadipocytes (11-13). As malignant transformation of fat tissue has also been reported, fine-needle aspiration cytology should not be avoided in diagnostic work-up (14,15).

Although the etiology of Madelung's disease is unknown, the present case confirms its strong association with alcoholism. In fact, alcohol intake of more than 80 g *per* day for at least 10 years, which has been found in up to 90% of cases described in the literature, was also present in our patient (16-20). Alcohol might act as a cofactor in the development of lipomas in several ways. It may reduce the number of β-adrenergic receptors, thus hindering the lipolytic effect of norepinephrine; it hampers β-oxidation leading to decreased lipolysis and promotes lipogenesis (21,22). However, some benign symmetric lypomatosis patients without any history of alcohol consumption have also been reported (23).

Kodish *et al.* have postulated that the fatty masses result from hypertrophy of the brown adipose tissue (24). These masses are the result of an abnormality in the synthesis of intracellular cyclic adenosine monophosphate (cAMP) induced by the autonomy of fat cells in BSL. The main defect is in the catalytic unit of adenyl cyclase, and alcoholism seems to decrease beta-adrenergic receptors and to induce a disturbance in the mitochondrial DNA in the adipose tissue, peripheral nerve, muscle and central nervous system (25-28). Several BSL cases with A8344G mutation of mitochondrial DNA have been reported (29,30).

Polyneuropathy described as a sensory, motor and autonomic dysfunction and detected in about 85% of patients with this disorder was not present in our patient. It usually develops several years after the lipomas have appeared. Histological studies show loss of larger myelinated cells, without demyelination or axonal degeneration present in chronic alcoholism. No cases of regression or improvement have been reported, and there is no effective treatment yet (27,31).

Although described in the literature, we found no association with hyperlipoproteinemia, hyperuricemia, hyperthyroidism or diabetes mellitus either (20,32).

Recently, multiple subcutaneous lipomas were found in patients with HIV-1 infection treated with indinavir or lamivudine, and an effect of protease inhibitors on lipid metabolism has been suggested (33). Some authors also suggest that two different types of fat tissue may play a different role in the lipodystrophy syndrome, with one type of fat tissue being involved in triglyceride accumulation, and the other one in lipid mobilization. They postulate that alcohol, protease inhibitor and steroid hormones both in the "buffalo hump", a clinical aspect of the lipodystrohy syndrome during HIV infection and in Madelung's disease, could activate fat storage in the "brown memory" adipocytes inhibiting white adipocytes (34). The biochemical activity of subcutaneous fat tissue lying around the neck and between the shoulders could be transformed into brown-like adipose tissue by these metabolic triggers. However, the failure to detect brown adipose tissue uncoupling protein messenger RNA in Madelung's disease suggests that the masses of multiple symmetric lipomatosis are not functional brown adipose tissue (34,35).

Furthermore, isolated subcutaneous fat accumulation is not necessarily accompanied by insulin resistance. Haap *et al*. report on higher insulin sensitivity, circulating adiponectin and HDL, and lower LDL levels in patients with Madelung's disease compared to those with simple obesity (36). This is in accordance with our patient's data, showing normal insulin and glucose metabolism, increased HDL and lower LDL level. It seems that fat depots in Madelung's disease may be metabolically innocent, possibly by preventing lipotoxicity. In fact, a remarkable analogy to thiazolidinedione action, which also promotes subcutaneous fat deposition while improving insulin sensitivity and glucose tolerance, was noticed (37).

Regarding the treatment of Madelung's disease, dietary management does not help and abstinence from alcohol may only prevent further progression in the size of fat masses. Lipectomy and liposuction are the treatments of choice. Liposuction allows surgery under local anesthesia and avoids the use of general anesthesia in patients with chronic alcoholism and possible liver lesions who are susceptible to hemorrhage (38). The use of ultrasound-assisted liposuction has also been reported (39). The location of the lipomas should be carefully considered before choosing one technique over another. Medical therapy with thyroid extracts, vitamins and salbutamol (for lipolysis stimulation) has not been proved to be effective (40).

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