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A Chinese patient with Madelung's disease and alcoholic cardiomyopathy: a case report and literature review

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Abstract. – BACKGROUND: Madelung's disease is a rare disorder characterized by massive deposits of excess subcutaneous fat around the neck, shoulders, arms, and other parts of the body. It has a high prevalence among middle-aged alcoholic men in Mediterranean countries and a low incidence in Asian populations. Although patients with Madelung's disease are often associated with a variety of alcohol-induced metabolic disorders, the comorbidity of alcoholic cardiomyopathy is rarely reported, probably because of its low incidence or neglect by clinicians.

CASE REPORT: A 67-year-old man with a 10-year history of soft fat masses in the neck developed chest tightness and shortness of breath on exertion for the past 2 years. Laboratory tests revealed elevated γ-glutamyl transferase, glucose intolerance, hyperuricemia, hyperlipidemia, and anemia. Computed tomography of the neck showed symmetric nonencapsulated fat deposits, mainly in the anterior cervical regions. Echocardiography showed left heart enlargement and severe global left ventricular systolic dysfunction with an ejection fraction of 31%. Coronary angiography revealed 40-50% stenoses of the left anterior descending and right coronary arteries. After the exclusion of other causes of dilated cardiomyopathy, the patient was finally diagnosed with type I Madelung's disease and alcoholic cardiomyopathy. He underwent lifestyle changes, including reducing his alcohol intake, and received full pharmacological treatment for heart failure. One and a half years later, his cardiac function was partially restored, and all metabolic abnormalities improved except for elevated liver enzymes.

CONCLUSIONS: Alcohol use disorder should be assessed in patients with newly diagnosed Madelung's disease. Screening for alcoholic cardiomyopathy in alcoholic patients with Madelung's disease is necessary for early detection of cardiac abnormalities and intervention to improve the prognosis of this group of patients.

Key Words:
Madelung's disease, Alcohol abuse, Alcoholic cardiomyopathy.

Introduction

Madelung's disease (MD), also termed multiple symmetric lipomatosis or Launois-Bensaude syndrome, was first described by Brodie in 1846 and then systematically summarized by Otto Wilhelm Madelung in 1888[1,2]. The disease is clinically characterized by the presence of diffuse and symmetrical fat deposits in the superficial and/or deep subcutaneous fascial spaces of the neck, shoulders, and other trunk parts[3]. The incidence of MD is 1:25,000, and it predominantly affects middle-aged white males, especially those from the Mediterranean region[4]. A few cases affecting children and women have also been reported[5,6].

Approximately 60-90% of patients with MD have alcoholism[7], and an association between chronic alcohol consumption and lipoma formation has been suggested. Alcohol is thought to be a facilitator, as it can impair lipolysis by reducing the number of beta receptors and disrupt mitochondrial function by promoting premature oxidation of mitochondrial DNA, resulting in excessive fat accumulation in adipocytes[8]. MD is often associated with other alcohol-related metabolic disorders such as diabetes mellitus, hyperuricemia, hyperlipidemia and liver disease[9]. However, the comorbidity of alcoholic cardiomyopathy (ACM) in patients with MD has rarely been reported. We searched PubMed and Web of Science databases and found only one literature report on MD combined with ACM. Herein, we describe a

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67-year-old male alcoholic patient who presented with excessive symmetrical fat mass around the neck, complained of exertional chest tightness and shortness of breath, and was ultimately diagnosed with MD and ACM. After reducing alcohol intake and receiving full pharmacological treatment for heart failure, his cardiac function was partially restored, and all metabolic abnormalities improved except for elevated liver enzymes.

Case Presentation

A 67-year-old man presented with soft tissue masses in the neck that had developed over a period of 10 years (Figure 1). He had been drinking 500 ml of liquor and smoking 20 cigarettes per day for more than 50 years. For the past 2 years, the patient has experienced chest tightness and shortness of breath on exertion. Over the past 5 months, he felt that the cervical lipomatosis was gradually increasing in size, and his chest tightness and shortness of breath were worsening. He had no dysphagia and no sensory or motor abnormalities in the distal extremities. He denied any history of preceding viral disease or toxic exposure, and there was no similar condition in his family. His siblings were alive and healthy.

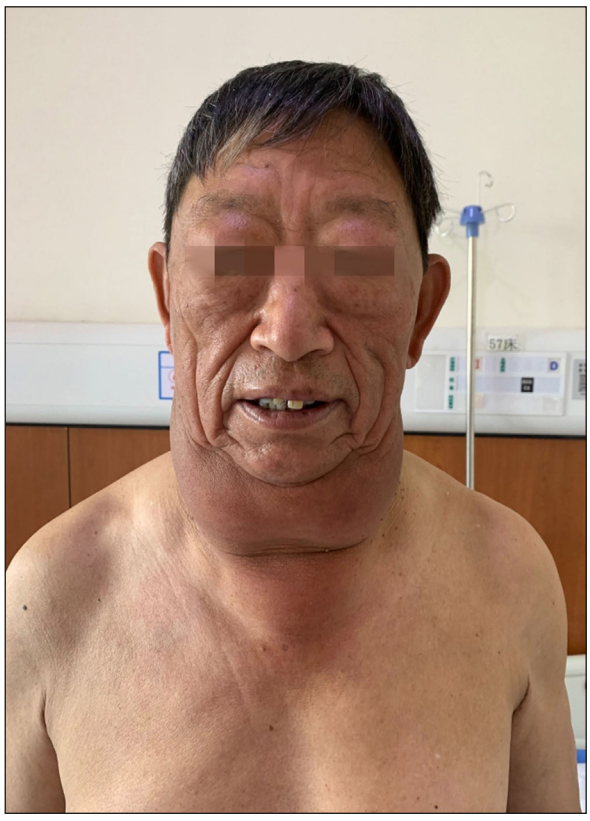

Figure 1. The figure shows the patient with anterior cervical lipomatosis.

He was slightly overweight, with a body mass index of 24.1 kg/m^2 and a waist circumference of 91.5 cm. His blood pressure was normal. Physical examination revealed excessive symmetrical soft tissue masses accumulated around the neck, forming a typical "horse collar". His apical beat was markedly shifted to the left with a loud systolic murmur of mitral regurgitation. His lower extremities were pitting edema. Laboratory tests showed elevated γ-glutamyl transferase, hyperuricemia, hyperlipidemia, and anemia (Table I). Cardiac markers were negative for troponin I and slightly elevated for brain natriuretic peptide. Blood gas analysis showed a significant decrease in oxygen partial pressure to 76.8 mmHg (reference: 83-108 mmHg). Tests for tumor markers were normal except for a slight elevation in cancer antigen 19-9 (CA 19-9). He was diagnosed with impaired glucose tolerance based on an oral glucose tolerance test. Thyroid function, cortisol, autoimmune markers, coagulation indicators, hepatitis virus, and other viral tests were within normal limits. Computed tomography (CT) of the neck showed symmetrical nonencapsulated fat deposits dispersed over the superficial and deep fascial spaces of the anterior cervical region (Figure 2A), and supraclavicular fossa and the intermuscular spaces in the posterior cervical region were also enveloped by hyperplastic adipose tissue (Figure 2B). The trachea was centered and there was no sign of compression. Chest CT showed cardiac enlargement, fibrous nodules with calcification in the apicoposterior segment of the left upper lobe, and bronchiectasis of the right lung (Figure 3). The results of the electrocardiogram demonstrated sinus bradycardia with a rate of approximately 58 beats/min, right bundle branch block and ST-T segment changes indicating left ventricular strain. Echocardiography showed left atrial and ventricular enlargement, moderate mitral regurgitation, mild aortic regurgitation, and severe global left ventricular systolic dysfunction with an ejection fraction of 31% (Figure 4). He was then admitted to the Cardiology Department for heart failure management. In the cath lab, coronary angiography revealed 40-50% stenoses of the left anterior descending and right coronary arteries. Cardiac magnetic

Table I. Laboratory tests at the time of admission and follow-up findings.

Variable	At admission	Follow-up	Reference
Erythrocyte count (10^6/μL)	3.66	4.49	4.3-5.8
Hemoglobin (g/dl)	12.5	14.8	13.0-17.5
Hematocrit (%)	36.1	43.7	40-50
Albumin (g/dl)	3.5	4.7	4.0-5.5
Alanine aminotransferase (U/L)	30.26	33	9-60
Aspartate aminotransferase (U/L)	34.75	50	15-45
γ-glutamyl transferase (U/L)	137.5	203	10-60
Uric acid (mg/dl)	7.3	7.2	3.5-7.2
Creatinine (mg/dl)	0.81	0.73	0.64-1.25
Fasting blood glucose (mg/dl)	89	/	70-110
Glycated hemoglobin (%)	5.6	/	3.6-6.0
Total cholesterol (mg/dl)	251	213	<200
Triglyceride (mg/dl)	141	234	<150
Low-density lipoprotein cholesterol (mg/dl)	141	122	<130
High-density lipoprotein cholesterol (mg/dl)	69	77	>40
Brain natriuretic peptide (pg/ml)	101	/	0-100

resonance imaging (MRI) was recommended for differential diagnosis, but the patient refused for financial reasons.

Finally, he was diagnosed with type I Madelung's disease, impaired glucose tolerance, hyperuricemia, hyperlipidemia, hepatic dysfunction, and anemia. Nonsurgical treatment is recommended due to his poor cardiac function. He was advised to quit smoking and abstain from alcohol and was prescribed full pharmacological treatment for heart failure (an angiotensin-receptor neprilysin inhibitor, a sodium-glucose transport protein-2 inhibitor, an aldosterone antagonist, an anticoagulant, a statin, a diuretic). Lifestyle changes were also recommended, such as avoiding high-starch foods and sugary drinks and eating more fiber-rich foods and less refined grains and fatty meats. After being discharged from the hospital, the patient still had the urge to drink, and he cut back to drinking about 330 ml of beer per day, three times a week. After one and a half years of reduced alcohol intake and medication, the patient's symptoms of chest tightness and shortness of breath were relieved, and the

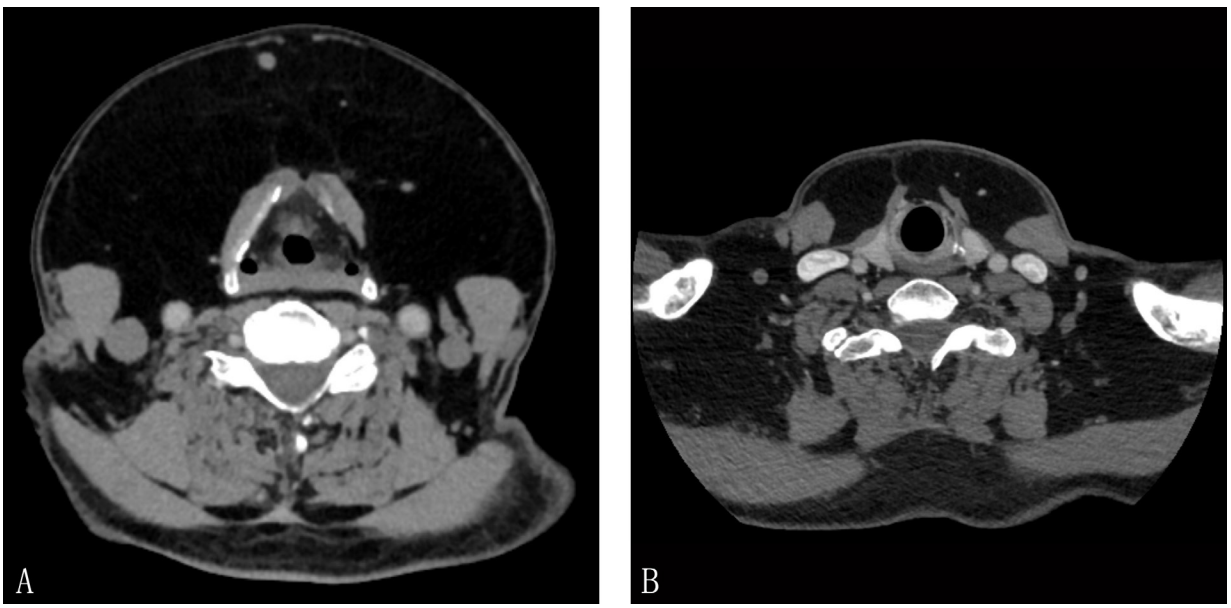

Figure 2. Cervical computed tomography showed symmetrical massive fat deposits in the anterior cervical (**A**) and supraclavicular (**B**) regions.

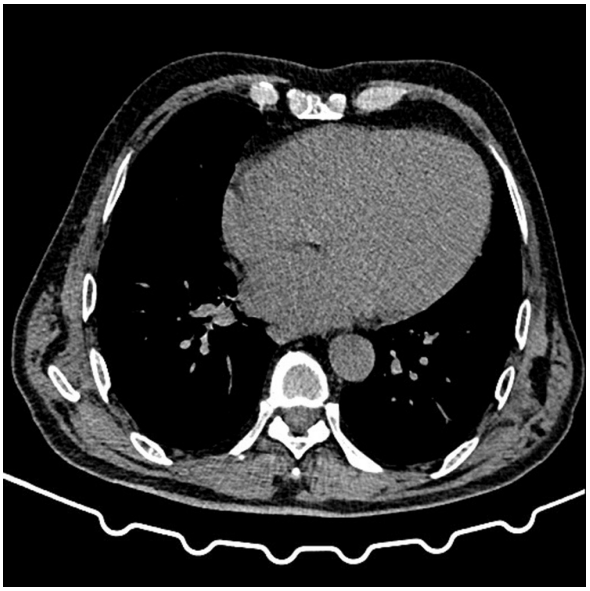

Figure 3. Chest CT showed an enlarged heart.

lipomatosis remained constant. The results of his repeated laboratory tests are shown in Table I. All metabolic disturbances improved except for elevated liver enzymes. The echocardiogram showed an improvement in ejection fraction from 31% to 39%; left ventricular dilatation and hypokinesia, although diminished, were still present on echocardiography.

Discussion

Madelung's disease (MD) is a relatively rare disorder involving a symmetric subcutaneous accumulation of nonencapsulated adipose tissue in various parts of the body[10]. According to the distribution of the fat masses, a classification into two types was proposed by G. Enze in 1984[11]. Type I, known as the "horse collar," is characterized by the distribution of subcutaneous fat masses mainly around the neck, shoulders, and upper back, and type II is characterized by excessive fat deposits in the abdomen and thighs. Later, Donhauser et al[12] divided MD into four subtypes: type I-localized type, type II-pseudoathletic type, type III-gynecoid type, and type IV-abdominal type. This patient was diagnosed with type I MD based on the pattern of fat distribution.

The exact mechanism of MD is unknown. A defect in adrenergic-mediated lipolysis of brown adipose tissue has been suggested as a mechanism for the abnormal fat distribution[13]. Disturbances in mitochondrial metabolism due to mitochondrial DNA alterations or respiratory chain dysfunction have also been implicated in the development of MD[14,15]. A mitochondrial *MTTK* gene variant has been reported in a Canadian family with MD[16], suggesting a matrilineal genetic predisposition to Madelung's disease.

MD is often associated with multiple metabolic disorders, including peripheral insulin resistance, hyperuricemia, hyperlipidemia, hypothyroidism, macrocytic anemia, and polyneuropathy. Upper respiratory tract cancer and other malignancies, such as lung and tongue cancer, have been reported in patients with MD[17-19]. It is unclear whether this is a result of the combined effects of nicotine and alcohol or a genetic predisposition of MD patients[20]. After a thorough evaluation, the patient was found to have glucose intolerance, hyperuricemia, hyperlipidemia, anemia, hepatic dysfunction, and alcoholic cardiomyopathy. Most of these were caused by alcohol abuse. Alcohol has been shown to have a negative inotropic effect on the

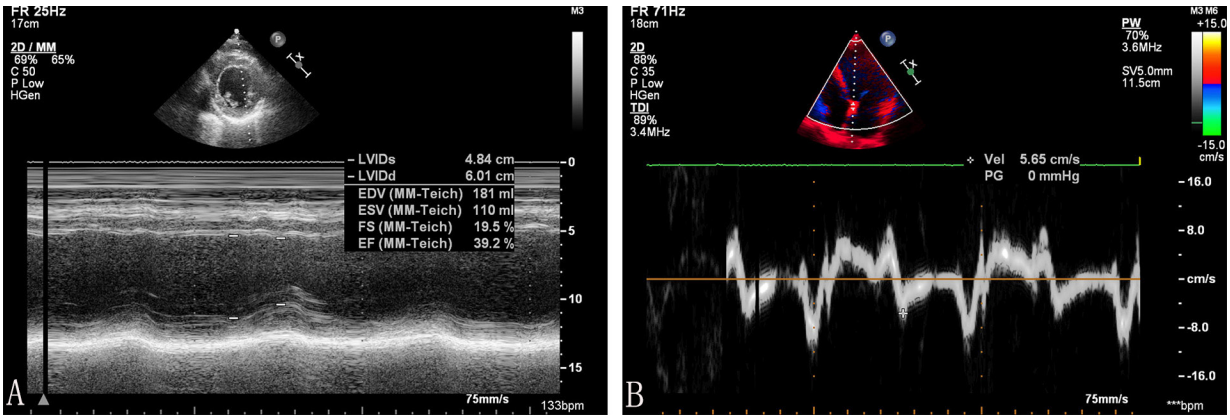

Figure 4. Cardiac ultrasound showed diffuse left ventricular systolic dysfunction (**A**) and mild mitral regurgitation (**B**).

myocardium[21]. This explains why this patient developed sinus bradycardia and left ventricular hypokinesis after years of heavy alcohol consumption. The patient's CA 19-9 levels were slightly elevated, but he was asymptomatic, and CT of the upper abdomen showed no abnormalities, so we advised the patient to follow up regularly.

MD should be differentiated from morbid obesity, Dercum's disease, Cushing's disease, neurofibromatosis, and salivary gland disorders[22]. CT or MRI are commonly used imaging modalities that can contribute to the preoperative evaluation and may be necessary in some cases for the differential diagnosis of MD[23]. Based on the typical appearance and imaging findings, the diagnosis of MD is clear in our patient.

Liposuction and lipectomy are the most widely used treatments for MD, but recurrence is common even with extensive intervention[24]. Alcohol abstinence is mandatory for patients with MD and may reduce the recurrence rate[25]; hyperplastic adipose tissue is minimally affected by dietary restriction and weight loss[24]. Oral fenofibrate or salbutamol have been reported to inhibit or even reverse the progression of lipomatosis in individual cases[26,27], but studies in larger patient populations are needed to verify their efficacy. This patient was finally treated non-surgically due to his chronic heart failure.

In fact, ethanol and its metabolites could exert their toxic effect on all the organs of the human body, such as the liver, the brain, the kidneys, and the stomach[28]. Alcoholic cardiomyopathy (ACM) is the most common form of alcohol-induced heart damage[29]. The reported incidence of ACM in patients with alcohol use disorders ranges from 21% to 32%[30]. The evidence for alcohol-induced cardiomyocyte toxicity is well documented. Chronic high doses of alcohol are associated with cardiomyocyte hypertrophy, apoptosis, and necrosis[31]. Furthermore, acetaldehyde, the active metabolite of alcohol, can impair cardiac excitation-contraction coupling, disrupt structural protein synthesis, and promote oxidative damage and lipid peroxidation[29]. In addition to genetic susceptibility, other factors such as electrolyte disturbances, nutritional deficiencies, or cocaine and tobacco exposure have been implicated in the development of ACM[32,33]. The symptoms of ACM are non-specific and similar to those of other causes of chronic heart failure, and the diagnosis of ACM depends largely on the exclusion of other causes of dilated cardiomyopathy[34]. The diagnosis of alcohol-induced cardiomyopathy in this patient was based on a clear history of alcohol abuse and the observation of improvement in cardiac function after reduction of alcohol intake, although not return to normal levels as reported in previous individual cases[21,35]. There is no evidence of antecedent viral infections or toxic exposure, and there is no family history of cardiomyopathy in this patient. In addition, the stenosis degree of the coronary arteries did not appear to be a primary cause of heart failure. The lack of evidence for other types of dilated cardiomyopathy indirectly supports the diagnosis of ACM.

Complete alcohol abstinence is the cornerstone of treatment for ACM[30]. Guillo et al[36] have found significant improvements in cardiac function when alcohol cessation is initiated before myocardial fibrosis. Guzzo-Merello et al[37] investigated the clinical characteristics and outcomes of 94 patients with ACM and found that the prognosis of patients who reduced their alcohol intake to <80 g/day was similar to that of total abstainers. However, the cut-off point for a safe level of alcohol intake is still unclear, so it is still necessary to achieve total abstinence. In addition to alcohol abstinence, patients should receive comprehensive medical therapy for heart failure. Implantable cardioverter defibrillator or heart transplantation should be considered in patients whose cardiac function deteriorates despite optimized pharmacological therapy[38]. After reducing alcohol consumption and taking comprehensive heart failure medications, the patient's left atrial and ventricular enlargement were significantly reduced. However, left ventricular systolic function recovered slightly. We speculate that the minimal improvement in cardiac function may be due to irreversible myocardial fibrosis resulting from long-term alcohol abuse or causative agents that are not completely eliminated. Failure to achieve optimal titration of an angiotensin-receptor neprilysin inhibitor and the absence of beta-blockers due to sinus bradycardia may be possible reasons. His pharmacological therapy was optimized, and a specialist in alcoholism was recommended. We will continue to follow up with the patient to monitor the progression of lipomatosis and recovery of cardiac function.

Conclusions

In conclusion, we believe that excessive alcohol consumption should be assessed in patients with newly diagnosed Madelung's disease. The

Alcohol Use Disorders Identification Test may help to identify those affected by harmful alcohol consumption[39]. In view of alcohol-induced cardiomyocyte toxicity, screening for ACM by cardiac ultrasound in patients with chronic alcohol abuse is necessary for early detection of abnormalities in cardiac structure and function so that interventions can be made to improve the quality of life of patients with MD. In addition, collaboration with alcohol addiction specialists may be helpful in identifying patients with alcohol use disorders and subsequent treatment of MD and ACM.

Ethics Approval
This study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013), and the protocol was reviewed and approved by the Ethics Committee of Qingdao Municipal Hospital (2023LSZD171).

Informed Consent
Written informed consent was obtained from the patient for participation in the study and publication of his clinical data and images.

Availability of Data and Materials
All data generated or analyzed during this study are included in this published article.

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Authors' Contributions
HZ collected the clinical information and drafted the original manuscript. XM obtained follow-up data and prepared all figures and tables that appear in the article. KY was mainly responsible for data organization. FZ analyzed the data and interpreted the results. SL conceived and designed the study, revised the manuscript, and approved the final version of the manuscript for submission. All authors reviewed and approved the final version of the manuscript.

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Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

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