CASE REPORT

State of diagnostic quandary solved by modern technology: a rare case of Madelung's disease

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Accepted 21 January 2016

SUMMARY

Madelung's disease is a neglected metabolic disease characterised by generalised multiple fatty tissue deposits. A 64-year-old Caucasian woman presented with generalised weakness and symptomatic hypoglycaemia with altered mental status. Physical examination showed very distinct physical characteristics with multiple lumps distributed over the upper body. Her neurological symptoms were solved by giving intravenous glucose and optimisation of medical treatment. Even though she had unique characteristics of Madelung's disease, many physicians, on several occasions, failed to recognise her 'hidden diagnosis'. This diagnostic uncertainty was able to be solved by searching the Internet for similar clinical features and images. This case demonstrates characteristics and unique features of a rare disease that can be seen in a female patient even though it is mostly found in males.

BACKGROUND

Madelung's disease (MLD) is a rare metabolic condition characterised by multiple symmetric accumulations of non-encapsulated fatty tissues throughout the body. Its aetiology is still unclear but there are some data documented in the literature of an association with chronic alcoholism. Owing to the fact that this is a rare disorder with few cases described in the literature, it was a challenging diagnosis to make. Diagnosis is made mainly by clinical examination, but imaging studies, including CT or MRI scan, can be used to confirm the disease. The latter, however, is often the preferred choice. Tissue biopsy may be necessary in some cases where suspicion of soft tissue malignancy is high—it will help to not only confirm the diagnosis but also rule out malignancy. We present a case of an elderly patient who presented with hypoglycaemia and multiple lumps throughout the body that were initially mysterious to the medical team but later identified as MLD.

CASE PRESENTATION

A 64-year-old Caucasian woman with a medical history of hypothyroidism and polyneuropathy presented to the emergency department, with symptomatic hypoglycaemia and altered mental status. She had experienced chronic progressive muscle weakness for 1 year, forcing her to stay at home most of the day. She denied illicit drug use and had not undergone recent trauma, even though she had chronic alcoholism. She had been drinking an unspecific amount of liquor for more than 40 years, and the last alcohol intake had been

about 2 weeks earlier. She was born in the USA and had no known family history of Mediterranean origin.

On examination, the patient was not oriented to time, and there was bilateral muscle weakness with 4/5 motor strength in the lower extremities. At first glance, we noticed multiple swellings all over the body—around the neck, upper back and upper extremities, which were very peculiar to the medical team. Her blood tests revealed <0.01 g/dL serum alcohol, a large amount of serum acetone and venous pH of 7.22, which were consistent with ketoacidosis due to chronic alcohol consumption. One common abnormality in blood tests seen in all her previous admissions was pancytopenia with no active bleeding. With the presence of hypoglycaemia, she was promptly given intravenous glucose with dramatic improvement of her mental status. Ultrasound (abdomen) showed markedly echogenic appearance of the hepatic parenchyma, compatible with fatty liver disease. CT scan of the head without contrast, CT scan of neck and chest X-ray showed evidence of increased subcutaneous fat accumulation in the shoulders, biceps and triceps. She had been aware of these deformities for 5 years, and they had neither physically nor aesthetically ever bothered her. With the knowledge and assistance of modern technology (the Internet), we were able to reach an accurate diagnosis of MLD. The patient was told the name of the disease, and its causes and management, including liposuction as well as alcohol abstinence, which may have stopped the progression of her lipomatosis. After extensive discussion, she decided to stop drinking alcohol but was unwilling to go for future surgical intervention.

INVESTIGATIONS**Blood test results**

The patient's repeated blood glucose was 135 mg/dL after intravenous glucose was given. Haemoglobin was 9.9 g/dL, white cell count (WCC) 4.2 K/cm, platelets 106 K/cm, serum alcohol levels <0.01 g/dL and glycated haemoglobin was 4.8%. Her basal metabolic profile showed serum sodium 132 mmol/L with calculated serum osmolality 272 mos/kg, a large amount of serum acetone, normal lactic acid level and 7.22 venous pH level, which were consistent with ketoacidosis due to chronic alcohol consumption. Her lipid profile was found to be 188 mg/dL total cholesterol, 87 mg/dL high-density lipoprotein, 83 mg/dL triglyceride and 84 mg/dL calculated low-density lipoprotein.

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To cite: Kyaw H, Grillo M, Lin AN, *et al.* *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213842

Her thyroid profile was within normal range—1.86 mIU/mL thyroid-stimulating hormone, 0.9 ng/dL free T4 and 0.5 ng/dL Total T3. Her metabolic panel showed 4 µg/dL cortisol and 1 ng/mL C-peptide, which were within reference range. She had a low vitamin D level with 19.1 ng/mL of vitamin D 25OH, normal B12 514 pg/mL and folate 13.8 ng/mL. HIV test was non-reactive and liver function test (LFT) was normal.

Urinalysis showed large leukocytes and was positive for nitrate with 10–20 WCC, suggestive of probable urinary tract infection.

Radiological tests and imaging

CT of the head and spine did not reveal any signs of intracranial pathology, including fracture, but there was a large lump on the patient's back, a so called buffalo hump (figures 1 and 2). She had multiple soft tissue masses throughout the body, including on the right arm (figures 3 and 4).

Ultrasound (abdomen) showed a markedly echogenic appearance of the hepatic parenchyma compatible with fatty liver disease.

DIFFERENTIAL DIAGNOSIS

Owing to the presence of altered mental status with documented hypoglycaemia and multiple lipomatosis lesions, the differential diagnosis included cirrhosis, metabolic encephalopathy, traumatic injury to the head, insulinoma, drug-induced lipomatosis (due to HIV medications), morbid obesity, Cushing syndrome and hypothyroidism. Cirrhosis was excluded by the patient's normal LFTs and normal ultrasound of the abdominal. Cushing syndrome and insulinoma could be easily ruled out due to normal cortisol and C-peptide levels. HIV blood test came back negative. Head trauma was unlikely with normal physical examination as well as a negative CT scan of the head.

TREATMENT

Given the presence of symptomatic hypoglycaemia, the patient was given intravenous glucose with serial glucose monitoring. Her mental status and glucose levels eventually returned to baseline. In laboratory tests, she had a confirmed urinary tract

Figure 1 CT scan of the neck demonstrating soft tissue lump (red arrow).

Figure 2 Illustrated tissue mass (fatty deposit) around the back of the neck, called a buffalo hump (red arrow).

infection with vitamin D deficiency, for which she was given vitamin D2 50 000 IU weekly and trimethoprim/sulfamethoxazole for 1 week. For MLD, the medical team opted for conservative management, as there is currently no definitive treatment. The patient agreed to stop consuming alcohol and begin supplemental vitamins, including daily thiamine and folic acid.

OUTCOME AND FOLLOW-UP

The patient's blood glucose had been stable throughout the hospitalisation. She was feeling better with the current treatment and was discharged home with outpatient follow-up planned.

DISCUSSION

MLD, also known as Launois-Bensaude syndrome, is a rare disorder of unknown aetiology, characterised by abnormal progressive growth and deposits of non-encapsulated diffuse, fatty tissues in the neck, shoulders, upper arms and trunk, and usually affects men in their 3rd–6th decades.¹ It is more frequently found in men, cases of chronic alcoholism, diabetes mellitus, lipid disorders and liver disease, and those of Mediterranean descent, whereas it is found to be less common in women and non-alcoholics.^{2 3}

Incidence of MLD is 1 in 250 000 (male–female ratio=15:1).⁴ It was first described by Sir Benjamin Brodie in 1846, then, in 1888, Otto Madelung reported the first case series of 33 patients. Launois and Bensaude published a second

Figure 3 Photograph of the patient showing multiple, massive, mass-like tissue proliferation in the neck and shoulders (red arrow); lipomatosis lesions were more prominent on the right compared to left side (red arrow).

Figure 4 Illustrated tissue mass (fatty deposit) around the right bicep area (red arrow).

case series of 65 patients in 1889 and, since then, there have been only about 250 cases reported in the literature.³ MLD can be classified into two-types according to layers of fat distribution. Accumulation of fat around the neck, shoulder blades, upper arms and upper back is defined as type- 1, mostly affecting men; while type-2 is found in men as well as in women, and is characterised by abnormal female fat accumulation throughout the body with the exception of the neck.^{2 5 6} It has been known by numerous names, such as multiple symmetric lipomatosis, symmetric adenolipomatosis, lipomatosis simplex indolens and benign symmetric liomatosis.^{3 7}

Although abnormal fat accumulation, called lipomatosis, is the cardinal feature of MLD, its underlying pathogenesis is still unknown. Appearance of MLD is quite similar to lipoma, which is a well circumscribed, localised accumulation of mature adipocytes in an encapsulated form. Lipomas are also the most common benign soft-tissue tumour of mesenchymal origin and can be found in all organs throughout the body. Histologically, they are with neither cellular atypia nor pleomorphism.⁸ Whereas MLD is characterised by multiple lipomatous tissues of normal or smaller-sized fat cells, in non-encapsulated form, and it has the ability to infiltrate the neighbouring structures. As the precise aetiology of benign lipomas is completely unknown, there is some speculation regarding the possible relationship between trauma and development of a lipoma. It is logical to think post-traumatic local inflammation promotes adipocyte proliferation⁹ but, to date, no definite link has yet been proven. Owing to the benign nature of MLD, it has probably been an underestimated diagnosis and mostly misdiagnosed as multiple lipomas.

The proposed pathogenesis of MLD is complex. The initial inciting event is occurrence of fatty deposits in the presence of functionally defective noradrenergic modulation that controls

proliferation and differentiation of brown adipose tissue (BAT), one of the embryonic residues.¹⁰ From molecular and cellular level analysis, MLD adipocytes can produce uncoupling protein (UCP)-1, a marker of BAT and product from interaction of β -adrenergic receptors and norepinephrine (NA), but NA cannot induce UCP-1 gene expression. Moreover, NA fails to improve nitric oxide (NO) production, leading to a reduction of antiproliferative effect on MLD adipocytes, resulting in a net adipogenic effect.¹⁰ Additionally, chronic alcohol consumption tends to decrease β -adrenergic receptors, thus leading to a disturbance of adrenergic control over interaction among UCP-1, NA and NO, which finally promotes lipogenesis rather than lipolysis.^{11 12} Brown adipose tissue is found abundantly in newborns, accounting for 60–70% of the total fat fuel for thermogenesis in response to cold temperatures. As with maturation of the sympathetic nervous system, brown fat atrophies and results in only small remnants when reaching into adulthood. In MLD, adrenergic denervation of adipose tissue, reduced lipolysis activity and many enzymatic changes in mitochondria level lead to excess accumulation of adipose triglyceride in the body and cellular hypertrophy with adipocyte hyperplasia.

Owing to its rarity, it is often difficult to recognise MLD. Our patient presented to the hospital due to hypoglycaemia and, during physical examination, was found to have abnormal fat distribution causing disfiguring aesthetic effects. At first, the medical team had not ascribed this patient's manifestations to MLD, and questioned the patient about the abnormal appearance. Subsequently, an Internet search was made, which helped to diagnose the disease. MLD is one of many rare diseases that may be easily missed if there is not a high degree of suspicion. On further investigation, complete blood count (CBC) showed pancytopenia without other abnormalities in the blood work. After careful electronic medical record review, the pancytopenia was found to have been documented 1 year prior, however, our patient had consistently refused to get further work up for it. Although the work up was not performed, it could have been partially explained by chronic alcoholism and a possible recent infection. There have been no documented case reports in the literature regarding an association of pancytopenia with MLD, to the best of our knowledge.

One case reported the very rare association of non-alcoholic woman with MLD, but she also had hepatic and pancreatic dysfunction along with glomerulonephritis. Even with multiple comorbidities, that patient had a normal CBC.¹³ Another case has been described in association with multiple fractures and haemoglobin of 12.1 g/dL without pancytopenia.¹⁴ A few cases have shown an association with chronic alcohol use and obstructive sleep apnoea, but none with mention of pancytopenia.^{2 3 15–17}

Until now, there has been no definitive treatment, with very few options to offer these patients. Medical treatment has a very limited role in this disease. It should be emphasised that patients with MLD should stop drinking alcohol. Surgery, such as liposuction, is another option—for removal of pre-existing lipid collections to relieve any compression symptoms. Although Enzi *et al* reported that MLD is associated with significant morbidity, MLD can rarely transform into liposarcoma, and there are only two documented cases in the literature.^{6 18 19} One salient point we would like to make in this case, was failure to get this 'hidden diagnosis' during previous hospital admissions, even though the patient had unique physical characteristics. This case highlights the use of the Internet as an aid to diagnosis, which can be helpful when a clinician is confronted with such a rare disease.

Learning points

- Madelung's disease is a very rare case presentation, especially in a female patient.
- It is usually more common in men, and associated with chronic alcoholism, diabetes mellitus, lipid disorders, liver disease and Mediterranean ancestry.
- If an abnormal body habitus unfamiliar to the clinician is seen it should always be investigated.
- Do not hesitate to use the Internet as an aid in the diagnosis of a rare disease.
- No definitive treatment is presently available for Madelung's disease, however, there are some very limited treatment options, including alcohol abstinence and liposuction.

Contributors HK was involved in conception of the idea, manuscript preparation, assay analysis and interpretation. ANL was involved in patient care and manuscript preparation. MG was involved in manuscript preparation, correlative assays and interpretation. D AK was involved in conception of the idea, assay analysis and proof reading. All the authors approve the submitted manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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