CASE REPORT

The endocrine and metabolic evaluation of benign symmetrical lipomatosis: a case report and literature review

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Abstract

OBJECTIVE: Benign symmetrical lipomatosis (BSL) is a rare disease characterized by the presence of multiple, symmetric and nonencapsulated fat masses. Alcoholism is observed in nearly 90% patients. However the etiology of this disease is still unclarified. BSL is very rare in Chinese people. Herein we described the endocrine and metabolic status of a patient with typical BSL. We also discussed the clinical manifestation, etiology, diagnosis and treatment for BSL.

RESULTS: Hyperuricemia and abnormal liver enzyme levels were observed in this case. However insulin sensitivity and function of the thyroid, adrenal glands and pituitary were all normal. The insulin sensitivity was assessed by the hyperinsulinemic euglycemic clam.

CONCLUSIONS: Although an association had been found between BSL and some endocrinological or metabolic disorders including abnormal glucose tolerance, excessive secretion of insulin, hyperuricemia, and so on, they were not specific for BSL. It is necessary to delvelop into the pathogenesis of BSL further.

Abbreviations:

BSL	- benign symmetrical lipomatosis
MSL	- multiple symmetrical lipomatosis
BMI	- body mass index
ACTH	- adrenocorticotropic hormone
OGTT	- oral glucose tolerance test
FSH	- follicle stimulating hormone
LH	- luteinizing hormone
PRL	- prolactin
T	- testosterone
E2	- estradiol
FT3	- free triiodothyronine
FT4	- free thyroxine
TT3	- total triiodothyronine
TT4	- total thyroxine
TGAb	- thyroglobulin antibody
TPOAb	- thyroid peroxidase antibody
TRAb	- thyroid stimulating hormone receptor antibody
TSH	- thyroid stimulating hormone
MRI	- magnetic resonance imaging
UFC	- urinary free cortisol
UCP1	- uncoupling protein1
BAT	- brown adipose tissue
NA	- noradrenaline
iNOS	- inducible nitric oxide synthase
MEN1	- mutiple endocrine neoplasia type1
CT	- computerized tomography
PPARα	- peroxisome proliferator-activated receptor

INTRODUCTION

Benign symmetrical lipomatosis (BSL), also named as Madelung's disease, Launois Bensaude disease, or multiple symmetrical lipomatosis (MSL), was first described by Benjamin. After that, Madelung in 1888 and Launois and Bensaude in 1898 characterized this disease. BSL is a rare metabolic disorder of fatty tissue characterized by abnormal adipose tissue accumulation, and the etiology is still unclarified completely (Smith *et al.* 1998). Patients usually refer to dentofacial surgery for cosmetic disfigurement. If the masses are large enough to produce symptoms of mass effect, patients usually complain of dyspnea and dysphagia. So most reported patients were submitted to surgical treatment. BSL is very rare in Chinese people. Herein we described the endocrine and metabolic status of a patient with typical BSL. We also discussed the clinical manifestation, etiology, diagnosis and treatment for BSL.

PATIENTS AND METHODS

Case report

A 51-year-old man was admitted to the Department of Endocrinology, complaining of progressively abnormal lipohypertrophy for 7 yrs. The excess fat tissue mainly distributed in his upper arms, cervical, bilateral breasts and upper back areas, without swelling or tenderness. The patient had no complaints of dyspnea, dysphagia or any problems with sensory or motor neuropathy. He had a 20-year history of heavy smoking and heavy drinking, with a 2-year history of gout. Family history did not reveal relatives with similar disfigurements.

Physical examination showed height 159 cm, weight 70 kg, body mass index (BMI) 27.7 kg/m^2 , blood pressure 120/70 mmHg. The patient had multiple areas of large lipomatous accumulation overlying the upper arms, the neck, and the upper back, contrasting the slim appearance of the lower arms and legs like "pesudoatheletic" appearance. (Figure 1A,B,C and Figure 2)

Laboratory studies

Biochemical and Endocrine tests: thyroid and gonadal function were normal. The diurnal rhythm of adrenocorticotropic hormone (ACTH) and cortison were abnormal. However 24-hour UFC level was within normal range, and 1 mg dexamethasone midnight suppression test showed cortison level was suppressed less than 50 nmol/L (Table 1). Results of 75 g oral glucose tolerance test (OGTT) were normal (Table 2). Relevant normal laboratory values included blood glucose, urea nitrogen, creatinine, electrolytes. He also had a normal lipid profile. Gammaglutamyl transpeptidase was 276.7 (normal range, 0–50 IU/L), alanine aminotransferase 50.8 (0–40 IU/L), blood uric acid 559.1 (104–144 μmol/L). Thyroid function: total triiodothyronine (TT_3) 2.32 (1.01–2.95 nmol/L), total thyroxine (TT_4) 85.0 (55.34–160.88 nmol/L) , free triiodothyronine (FT_3) 5.08 (2.76–6.3 pmol/L), free thyroxine (FT_4) 17.0 (10.42–24.32 pmol/L), thyroid stimulating hormone (TSH) 2.06 (0.35–5.5 mU/L). Gonadal hormons: testosterone (T) 21.64 (8.4–28.7 nmol/L), estradiol (E_2) 114.67 pmol/L, LH 6.68 (1.5–9.3 IU/L), prolactin (PRL) 7.97 μg/L, follicle stimulating hormone (FSH) 7.21 (1.4–18.1 IU/L). The presence of thyroid autoantibodies such as thyroglobulin antibody (TGAb) and thyroid peroxidase antibody (TPOAb) and TSH receptor antibody (TRAb) were negative.

RESULTS OF THE HYPERINSULINEMIC EUGLYCEMIC CLAMP

Beginning: blood glucose 4.48 mmoL/L, insulin level 2.90 mU/L,
End: blood glucose 5.08 mmoL/L, insulin level 96.9 mU/L,
at steady-state, mean value of blood glucose was 4.80 ± 0.17 mmol/L, the coefficient of variation was 3.54%. The M value (amount of glucose infused mg/kg/min) was 10.60 mg/kg/min (normal range: <11.56 ± 1.74 mg/kg/min), indicating normal insulin sensitivity.

Radiological analysis

Abdominal ultrasound showed chronic liver damage. Mammary gland ultrasound showed obvious thickening of the fat level.

Histological analysis

Histological (HE, original magnification × 100) analysis of fatty masses on upper arms biopsy revealed unencapsulated, lipomatosus hyperplasia fatty tissue, confirmed BSL (Figure 3).

Therapy

After admission, the patient was diagnosed as having benign symmetrical lipomatosis, hyperuricemia, liver dysfunction. Weight loss, abstinence of alcohol and cessation of smoking were recommended. Benzbromarone and polyene phosphatidylcholine capsules were administered to this patient for hyperuricemia and liver dysfunction. The patient declined to undergo further intervention of the affected areas, such as lipectomy or liposuction.

DISCUSSION

Benigh symmetrical lipomatosis (BSL) is a rare metabolic disorder of abnormal fatty accumulation, which affects more frequently men aged 30–60 years old, with a male-to-female ratio of 15: 1 to 30: 1. However a child madelung's disease has been reported recently (Shetty *et al.* 2007). It occurs most frequently in men from Mediterranean, with an incidence of about 1 : 25 000 in Italian men population (Parviz *et al.* 2006), but is very rare in Chinese people. Most cases have no family history,

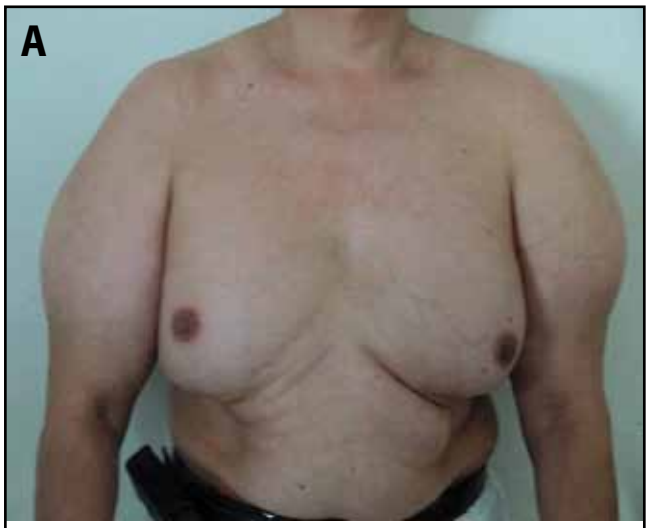
however some researchers think heredity and genetic influences play a role in this disease (Morinaka *et al.* 1999). Payne (Payne, 2000) reported a case of Madelung's disease with a family history of the brother and the grandchild of the patient.

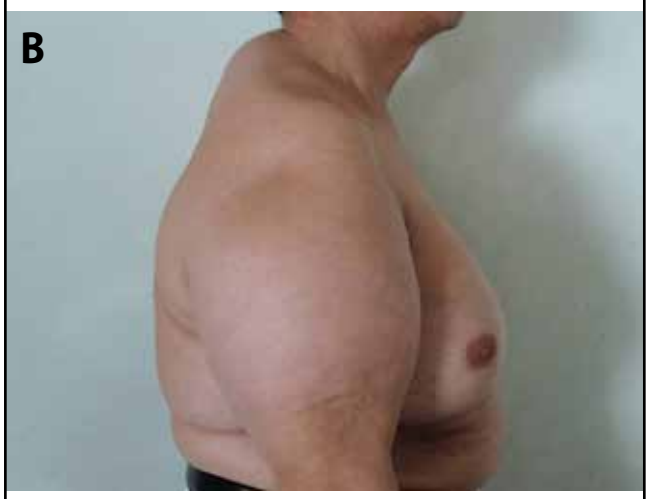
Pathogenesis

The etiology of this disease is unknown. Some pathogenesis are often described which are concomitant but not specific for the BSL, such as alcoholic abuse, liver dysfunction, malignancy of upper respiratory tract, endocrinological or metabolic disorders, rare hereditary diseases. However, only alcoholic abuse is confirmed to have a role in the pathogenesis of BSL. According to the literature, 60% to 90% of patients with BSL have a history of alcoholism, 60% are overweight. It is presumed that alcoholic abuse might change the normal lipid metabolism to some extent (Morinaka *et al.* 1999). Brown adipose tissue (BAT) is a specialized form of adipose tissue whose function is opposite to classical white fat function. As a thermogenic tissue it is a site of energy dissipation in contrast to the energy storing white fat. BSL is thought to be the result of a defect in catabolism of BAT. The main defect is in the catalytic unit of adenyl cyclase. Cell culture studies on MSL adipocytes showed a defective lipolytic response to catecholamines leading to an accumulation of triglycerides (Brackenbury & Morgan 1997). And alcoholism seemed to decrease beta-adrenergic receptors (Brackenbury & Morgan 1997). The uncoupling protein1 (UCP1), a protein unique to brown adipocytes, is central to uncoupling of brown fat mitochondrial respiratory chain, which is the mechanism of heat production in this tissue. UCP-1 could be found in the mitochondria of brown adipose tissue. Cell culture studies revealed the expression of UCP-1 could not be induced by noradrenaline (NA) in MSL adipocytes. In addition, the expression of inducible nitric oxide synthase (iNOS) could not be enhanced by NA either, which resulted in a decrease in the antiproliferative (Nisoli *et al.* 2002). Another theory maintained mitochondrial dysfunction should be the reason of BSL, which result in a decreased responsiveness of lipocytes to adrenergic stimulation (Urso & Gentile 2001). There are two types of fatty tissue involved in triglyceride accumulation or lipid mobilization. The biochemical activity of fat in different areas of the body may be transformed by metabolic triggers and drugs, such as alcohol or protease inhibitors. Steroid hormones may also lead to fat accumulation. In one case report, the rate of lipolysis in lipomatous tissue was elevated, with a preferential triglyceride fatty acid uptake (Nielsen *et al.* 2001) . Heredity and genetic influences are also thought to be invovled in this disorder. Multiple mtDNA deletions as well as single large-scale mtDNA deletions were reported to be found in familial and sporadic BSL patients. Point mutations have also been described, the most common of which was a base pair 8 344 mutation in the tRNA gene of mitochondrial DNA in patients with myoclonic epilepsy and ragged-red fiber disease (Klopstock *et al.* 1994).

Clinical features

BSL is characterized by subcutaneous encapsulated fat accumulations of the parotid region ("hamster cheeks"), cervical region ("horse collar"), posterior neck ("buffalo hump"), the hands, forearms, crural regions, and the central part of the face is usually not affected. Patients usually have no symptoms except cosmetic disfigurement .Because of aesthetic and social reasons, patients usually consult plastic or dentofacical surgeons. In some cases, the masses may be large enough to cause compression symptoms, including dyspnea, dysphagia, and dysphonia. In serious cases, tracheostomy has been performed emergently to relieve airway obstruction. The fatty masses often grow slowly over a long period, but in some cases, there was a faster development growth of adipose tissue (Vargas *et al.* 2000). Today at least two clinical phenotypes are recognized (Enzi 2000). In 1984, Enzi distinguished these two types, type 1 BSL affects primarily men and is characterized by fat accumulation around the neck, nape of the neck, upper back, shoulders, and upper arms. Type 2 affects both men and women, producing an exaggerated female fat distribution in the upper back, deltoid region, upper arms, hips, and upper thigh region. In this case ,the patient presented a pseudoathletic appearance because of the lipomatous distribution. According to the classifications it could be regarded as type I. Findings have shown that BSL are associated with some metabolic disorders including hyperuricemia, gout, abnormal glucose tolerance, excessive secretion of insulin, renal tubular acidosis, liver disease, and dysfunction of the thyroid, adrenal glands, pituitary, and testicles. However, no specific relation with the disease has been observed (Raul *et al.* 2004). It was reported that BSL had been found as only non-endocrine tumors in nearly 10% casess of mutiple endocrine neoplasia type1 (MEN1) (Morelli *et al.* 1995). MEN1 is a rare hereditary endocrine tumor syndrome characterized mainly by tumors of the parathyroid glands, endocrine gastroenteropancreatic tract and pituitary, and over 20 different combinations of endocrine and non-endocrine manifestations have been described. Alcohol-induced hepatopathy might be a main concomitant of BSL, which was already described by Launois and Bensaude. Häuptli presumed that the elevation of liver enzyme may be induced by a direct effect or a toxic influence on the fat metabolism of ethylic alcohol (Goetze *et al.* 2008). Neurologic involvements have been described, including sensory, motor and autonomic dysfunction. particularly peripheral neuropathy is frequent. About 85% of patients suffers from polyneuropathy, which occurs several years after the lipomas onset. Mitochondrial dysfunction may be responsible for the neuropathy (Feldman & Schabel 1995).





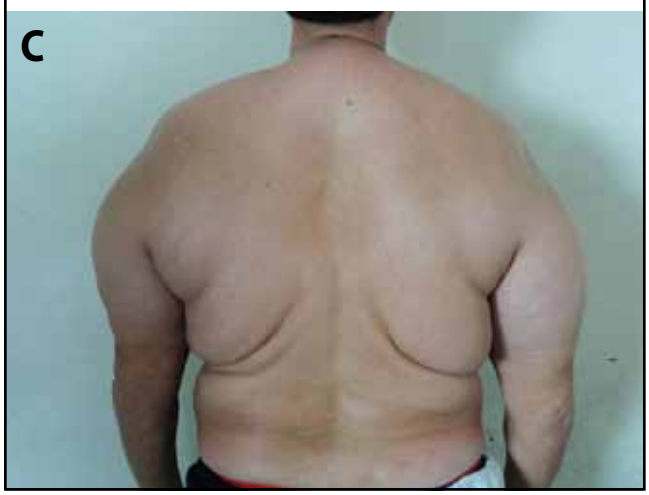


Fig. 1. A (anterior view) the marked, symmetrical accumulation of well demarcated adipose tissue in the upper arms and mammary region.
B (lateral view) prominent large fatty tissue formations around the supraclavicular regions and upper neck.
C (dorsal view) pseudoathletic appearance.

Fig. 2. Nearly normal-appearance legs.

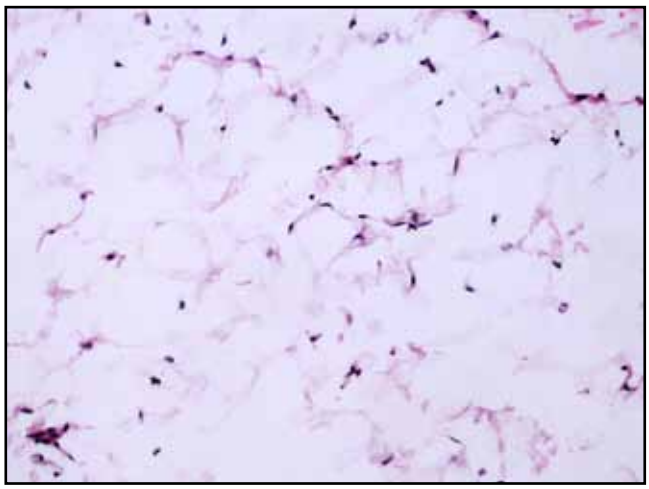


Fig. 3. Photomicrograph of excised specimen showed unencapsulated, lipomatosus hyperplasia fatty tissue, comfirmed BSL (hematoxylin and eosin, magnification × 100).

Diagnosis and differential diagnosis

The diagnosis of BSL may be established based on clinical picture, accurate history taking and physical examination. Imaging techniques such as computerized tomography (CT), ultrasound or magnetic resonance imaging (MRI) may be helpful for the diagnosis. Fine-needle aspiration may assist in the diagnosis. Cancer risk and the possibility of relation to any hereditary syndromes should be considered. Further image tests are recommended to perform to evaluate the extent of the masses and rule out other diseases.

The differential diagnoses include multiple diseases, such as familial multiple lipomatosis, Cushing syndrome, encapsulated lipomas, liposarcoma, simple obesity, neurofibroma, angiolipoma. Familial multiple lipomatosis occurs predominantly in men in their third decade. Unlike BSL, there is a higher likelihood of familial disorder, and the multiple encapsulated

lipomas are distributed over the arms, legs and trunk, however spare in the head, neck and shoulders (Ronan & Broderick 2000). Patients with cushing syndrome present central obesity, hypertension, impared glucose tolerance, purple strial, pigmentation. Biochemical analysis show elevated cortisone level, disappeared diurnal rhythm. Abnormal body shape changes similar BSL have been reported in HIV-infected patients on highly active antiretroviral therapy. Besides central adiposity and peripheral fat wasting, they also present hypertriglyceridemia, impaired glucose tolerance, and insulin resistance (Brinkman *et al.* 1999). It has been noted that nucleoside reverse transcriptase inhibitors block mitochondrial-DNA polymerase leading to failure of oxidative phosphorylation and subsequent metabolic disturbances similar to those in BSL. Thus, these syndromes may be considered a special variant of BSL.

Prognosis and treatment

Because of the difficulty in completely excising the mass, BSL recurrence is very common. The prognosis for BSL disease patients is generally good, and risk of degenerating into malignancy of these tumors is considered to be very low. But some authors consider the prognosis of BSL depends mainly on the concomtant presence of neuropathy. It has been reported that there was a mortality of 25.8% in BSL patients with neuropathy. Some authors even presumed that the disease activity is correlated to the polyneuropathy and not to alcoholism (Pollock *et al.* 1988).

Weight loss and cessation of alcohol use are recommended, but the effects on reversing or stopping progression of the disease is limited. For patients with aesthetic deformities, psychological problems with these deformities, and/or significant compression of the respiratory tract, surgical interventions including liposuction and lipectomy are recommened to relieve the symptoms. Liposuction techniques may offer a better alternative to standard surgical therapy in some cases and seems to be the best way to reduce cosmetic scarring. Medical therapy for benign symmetric lipomatosis has been studied, but the effect is controversy. Salbutamo, the Beta-2 agonist, has shown some success. The mechanism is thought to upregulate the expression of lipoma beta-receptors that would supplement the lipolytic pathway and help reduce the lipomatous mass (Kohan *et al.* 1993). The peroxisome proliferator-activated receptor (PPARα) is recently described as a suppressor of protein expressions, which is involved in the genesis of BAT and may function in keeping BAT in a quiescent state. Fibrates are efficient in the treatment of hyperlipidemia, also known as a PPAR α agonists. In one case, fibrates prevented adipose tissue from further increase during a follow-up of 14 months (Heike *et al.* 2008). However further studies need to be peformed to clarify whether fibrates is a new pharmaceutical option.

It is necessary to make further investigation of the pathogenesis of BSL to get a more precise knowledge for exploring new treatments that may decrease the high recurrence rate and complications.

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