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REVIEW

Multiple symmetric lipomatosis: A rare disease and its possible links to brown adipose tissue

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Abstract *Aim:* Aim of this study is an updated review of our case series (72 patients) as well as available literature on the Multiple Symmetric Lipomatosis (MSL), a rare disease primarily involving adipose tissue, characterized by the presence of not encapsulated fat masses, symmetrically disposed at characteristic body sites (neck, trunk, proximal parts of upper and lower limbs).
Data synthesis: The disease is more frequent in males, associated to an elevated chronic alcohol consumption, mainly in form of red wine. Familiarity has been reported and MSL is considered an autosomic dominant inherited disease. MSL is associated to severe clinical complications, represented by occupation of the mediastinum by lipomatous tissue with a mediastinal syndrome and by the presence of a somatic and autonomic neuropathies. Hyper-alphalipoproteinemia with an increased adipose tissue lipoprotein-lipase activity, a defect of adrenergic stimulated lipolysis and a reduction of mitochondrial enzymes have been described. The localization of lipomatous masses suggests that MSL lipomas could originate from brown adipose tissue (BAT). Moreover, studies on cultured pre-adipocytes demonstrate that these cells synthetize the mitochondrial inner membrane protein UCP-1, the selective marker of BAT. Surgical removal of lipomatous tissue is to date the only validated therapeutic approach.
Conclusions: MSL is supposed to be the result of a disorder of the proliferation and differentiation of human BAT cells.

Introduction

Multiple Symmetric Lipomatosis (MSL) was first described in 1846 by Sir Benjamin Brodie, who reported on two patients with symmetrical nucal lipomas [1]. In 1898 Madelung reported on three patients with symmetrical submental deposition of fat, the 'Madelung's collar' [2]. In 1898 Launois and Bençaude described in several patients this type of lipomatosis as 'symmetrical adenolipomatosis' [3]. MSL is a disease primarily involving adipose tissue, clinically characterized by the presence of not encapsulated fat masses, symmetrically disposed at the neck (83.3% of the male patients), dorsal area (55%), mammary

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and subcutaneous abdominal areas (35%), upper limbs (54.1%), lower limbs (28%). Distal segments of arms and legs are spared.

Since 1970's we collected clinical, laboratory and histological data of a large series of 72 MLS affected patients. In this review, we provide a complete description of our experience and the relevant data from the literature.

Clinical aspects

An approximate incidence rate of 1:25.000 has been calculated for MSL in the Italian population [4]. The disease was present in both men and women, with a ratio of 6 to 1 (61 males and 11 females) in our series. Mean age at onset was 42.5 ± 10.3 y (range 20–71) without significant differences in men and women [5]. Two types of distribution of the lipomatous tissue have been identified in MSL patients: type 1 (55 patients), in which the fatty tumors maintain the aspect of circumscribed masses protruding from the body surface, with atrophy of the uninvolved adipose tissue and with a normal Body Mass Index (BMI: 22.4 ± 1.6 kg/m^2) and type 2 (17 patients), in which lipomatous tissue progressively diffuses, involving subcutaneous fat layer and giving to the patients the appearance of a simple obesity, with a significantly higher BMI (32.4 ± 6.7 kg/m^2, $p < 0.001$) [4]. Females belong only to the type 2, with a mean BMI of 34.9 ± 6.7 kg/m^2 and a specific distribution of lipomatous tissue, characterized by a low occurrence of the Madelung's collar. Accumulation of lipomatous tissue at the thoracic inlet is less frequent in females [5]. Therefore the differential diagnosis of MSL and simple obesity in females might be more difficult.

An elevated daily alcohol consumption, mainly in form of red wine (from one to two and a half liters or more) is reported in 67 of MSL patients of our files and only 5 denied any alcohol intake.

Familiarity occurred in three cases in our files (two couples of siblings and in a father and son). According to Mc Kusik, MSL could be considered an autosomic dominant inherited disease [6].

MSL has been reported also in children. Bilateral supraclavicular, axillary and lower neck masses were found in a premature infant at birth, with attenuation values at computed tomography between fat and muscle, consistent with the peculiarity of brown adipose tissue [7].

A relevant clinical complication of MSL is the occupation of mediastinum and peri-pharyngeal spaces by lipomatous tissue, associated to laryngeal dislocation and compression (Fig. 1a), requiring a tracheostomy (Fig. 1b), and to a sub-mucosal infiltration of fatty tissue (Fig. 1c), with an otherwise unexplained cough. Signs of upper vena cava compression are also observed (Fig. 1b) [8–11]. It is noteworthy that medico-legal autopsies in adults with a positive record of heavy alcohol consumption give histological evidence of the presence of multi-locular adipose cells resembling brown adipose tissue around the thoracic aorta and the carotids. Unusual locations of lipomatous tissue in MSL have been reported in the tongue [12,13], in the scrotum [14] and in the retro-orbital space [15].

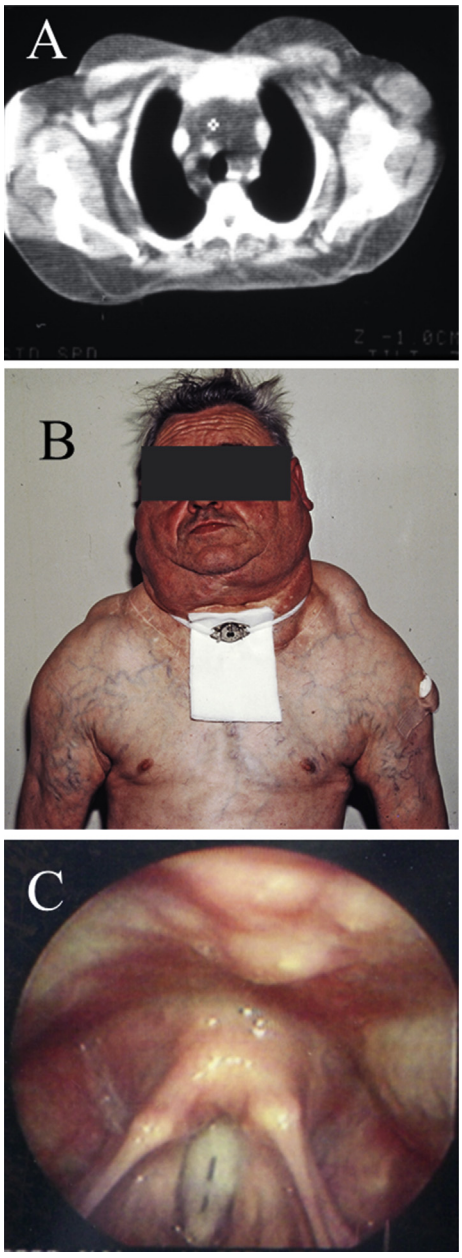

Figure 1 Fat accumulation at the thoracic inlet with laryngeal dislocation demonstrated by computed tomography in a patient with Multiple Symmetric Lipomatosis (A). The patient required tracheostomy during the course of the disease (B). Signs of vena cava compression are evident. Sub-mucosal pharyngeal fat infiltration was evident at video-laringoscopy (C).

A further relevant clinical aspect of MSL is the elevated prevalence of neurological abnormalities, described in MSL since 1937 [16,17]. Several MSL patients of our series presented signs and symptoms of peripheral motor and sensory neuropathies, mainly involving the lower extremities. By electromyographic study, an elevated prevalence of both somatic and autonomic neuropathies was demonstrated. Morphometry at electron microscopy of sural nerve biopsies in 5 non diabetic MSL subjects revealed a