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Rapidly progressive case of type I Madelung disease with bilateral parotid and minor salivary glands involvement

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ABSTRACT

Context: Madelung disease has been literally classified as a rare disease, more common in Mediterranean population. It is characterized by the presence of multiple symmetrical, non-capsulated storages of adipose tissue.

Case description: We present a 56 year old woman with a sudden unexplained progression of swelling in the neck and upper thorax region associated with severe dyspnea. She was admitted with angioedema in the Allergology Department. Radiology images identified a bilateral adipose degeneration of the parotid and minor salivary glands.

Conclusions: The diefinitive diagnosis concluded was Type 1 Madelung Disease. The decision was to keep the patient under periodic observation and if any deterioration takes place, surgical intervention will be taken under consideration. Despite non previous findings of Madelung disease in our population this case presented a challenge of emergency diagnosis.

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Madelung disease; swelling; Launois-Bensaude; parotid glands; adipose tissue

Case report

A female patient, 56 years old, BMI 41.6, self-presented to Accident and Emergency, complaining of shortness of breath, weakness, cough and sweating. Blood pressure was 130/80 mmHg. She had undergone hysterosalpingo-oophorectomy 20 years ago, and suffered from pulmonary disorders for more than a year. As a diagnosis of bronchoectasy had recently been made, and treated with an antibiotic, an antibiotic reaction was suspected.

On examination, there was a symmetric swelling around the neck, face and also deltoid region (Figure 1). On palpation the swelling felt warm and indurated, without any notable cutaneous alterations. 'Buffalo neck' was also evident (Figure 2). Sibilant crackles were noted during lung auscultation. Initial biochemical examinations showed normal U&Es and LFTs, with a slight increase in random blood glucose level, but normal HbA1c (Table 1). An epiaortic doppler-ultrasonography found a bilaterally normal blood flow, with an intima-media thickness <1 mm. There was evidence of a massive interstitial oedema in the neck tissues. A head, neck, chest and abdomen CT scan, without contrast, showed a perifocal proliferating swelling around the oropharyngeal region with thickness up to 7.6 mm. The lungs were normal. The patient was admitted with a suspected allergic oedema. Due to dyspnea and the high risk of suffocation, maxillofacial and otolaryngologist opinions were requested.

The following day other tests were performed. As obesity and the buffalo hump may reflect Cushing's syndrome, tests were arranged, as were autoantibody and immunological tests. A free larynx entrance and preserved vocal cords, without any inflammatory alterations, were observed on laryngoscope. A head-neck-chest CT with contrast found an increased symmetrically adipose tissue, in the subcutaneous area of the neck, parotid glands, supraclavicular region and larynx, which extended up to the sternocleidomastoid muscle and cervical area (Figure 3). The accumulated adipose tissue compressed the nearby structures and the adjacent muscles and vessels, which led to deformations. The fat mass had the same density as the normal adipose tissue and there were no inflammatory alterations. Thyroid gland had a normal structure. The lungs and the airways were normally structured, without pleural effusions. The thoracic and abdominal aorta, the superior and inferior vena cava were normal. An absent uterus and ovary glands (post hystero-salpingo-oophorectomy) were noted. At that point attention changed direction towards pathologies characterized by adipose tissue accumulation such as sphingolipidoses, lipomatosis etc.

A second round of blood tests are shown in Tables 2 and 3. Table 2 shows results of the cortisol suppression test. Three cortisol peaks were normal. A cortisol peak was also taken after a glucocorticoid dose, which was inhibited, confirming a well-functioning pituitary-

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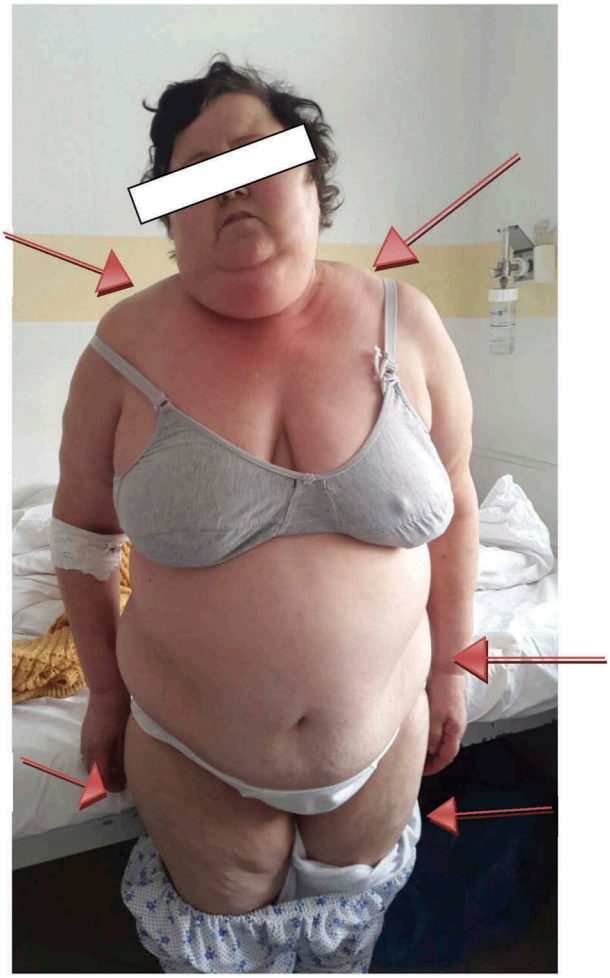

Figure 1. Picture of the patient showing a symmetric adipose accumulation around the neck, cervical area, abdomen and lower limbs.

Table 1. Blood results on admission.

Analyte	Patient's values	Reference range
RBG (mmol/L)	7.9	3.9–6.1
HbA1C (mmol/mol)	42	<46
AST (U/L)	35	10–40
ALT (U/L)	28	7–56
Uric Acid (µmol/L)	290	120–420
Urea (mmol/L)	3.3	2.5–7.1
Creatinine (µmol/L)	71	50–110
Sodium (mmol/L)	131	135–145
Potassium (mmol/L)	4.2	3.5–5.1
Chloride (mmol/L)	98	96–106

RBG: Random blood glucose

adrenal axis. The autoantibody/immunology tests (ANA, ANCA, C3, anti-dsDNA IgG) were all negative, although C1 inhibitor was 100 mg/dl (reference range 4–70 mg/dL). Other laboratory results are shown in Table 3. Thyroid function, total cholesterol and HDL were normal, but there was hypercalcaemia, a minor hypertriglyceridaemia, a raised CEA and raised fasting blood glucose, the latter suggesting impaired glucose tolerance. All are being further investigated.

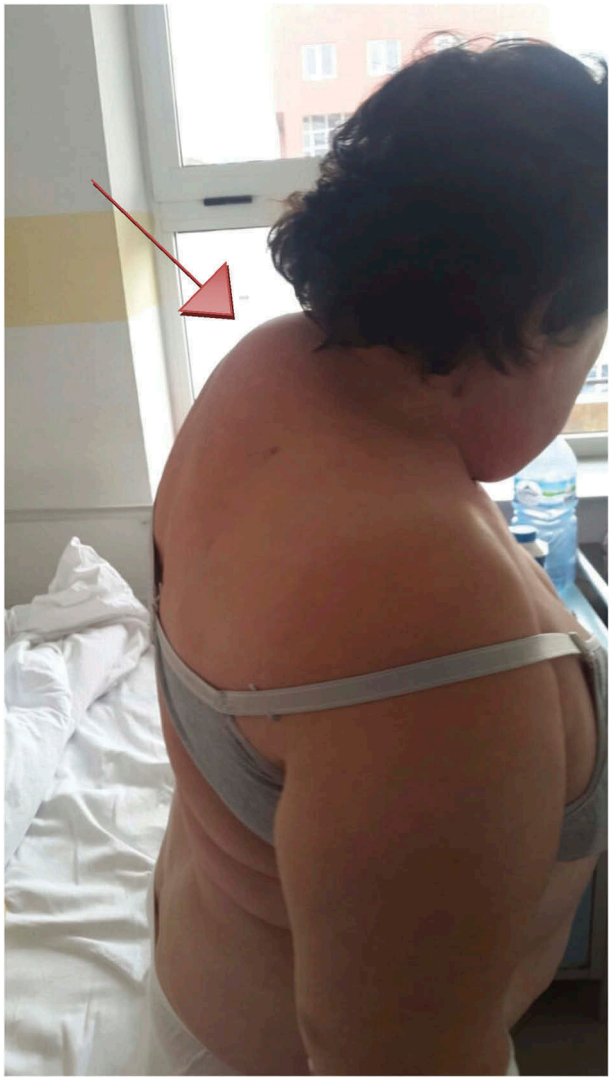

Figure 2. Picture of the patient showing a 'buffalo hump'.

Differential diagnoses

With the benefit of imaging and laboratory tests in addition to clinical data, different diagnoses were considered by the multidisciplinary team. With an appearance of a round face and abdomen and a gibbous deformity, Cushing's disease was the first to be considered, but thought unlikely because of striae absence, normal skin colouring, non hypotrophic limbs, and well-structured adrenal glands on CT. It was completely ruled out by a normal cortisol suppression test. Superior vena cava obstruction syndrome was also considered, a diagnosis characterized by facial edema, vasodilatation, respiratory problems, first described by William Hunter in 1757, in a patient with a syphilitic aortic aneurysm. The head-neck-chest tomography with contrast and ultrasound excluded vascular problems.

The replacement of parotid gland tissue with adipose tissue is a radiologic finding, which up to the present days

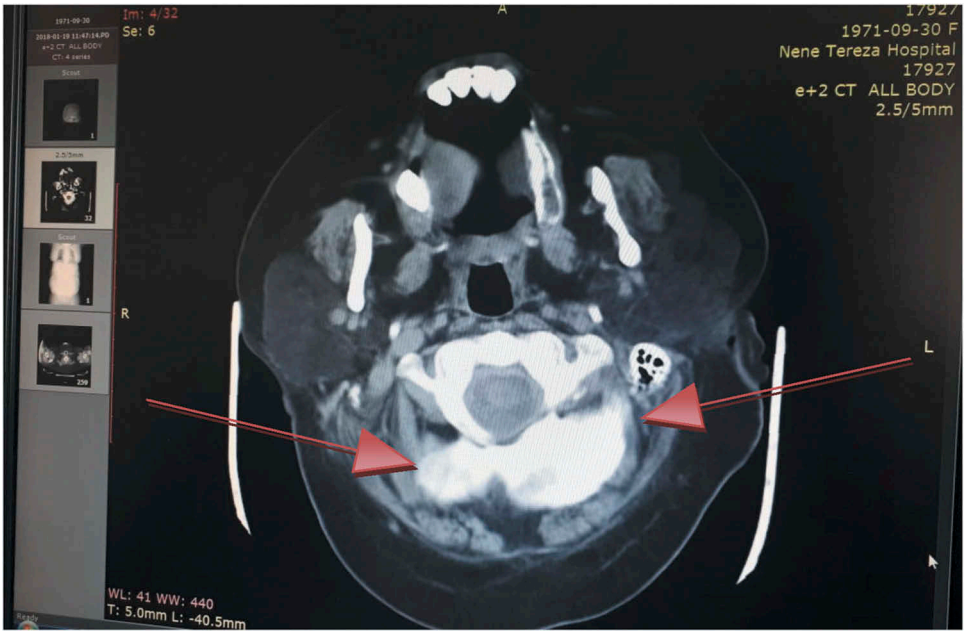

Figure 3. Axial CT image of the base of the skull showing adipose infiltration in the cervical area.

Table 2. Tests for Cushing's disease on day 2.

	Patient's values	Reference range
Cortisol at 8.00	150 nmol/L	170–635
Cortisol at 16.00	168 nmol/L	82–413
Cortisol at 20.00	121 nmol/L	82–413
Cortisol after 25 mg intra-muscular prednisolone	55 nmol/L	

Table 3. Blood results on day 2.

Analyte	Patient's values	Reference range
TSH (mIU/L)	0.56	0.4–4.8
Free T3 (pmol/L)	4.1	3.5–6.5
Free T4 (pmol/L)	17	13–27
Total cholesterol (mmol/L)	4.9	< 5.2
HDL (mmol/L)	0.76	> 0.91
Triglycerides (mmol/L)	1.95	0.45–1.71
Total Calcium (mmol/L)	2.9	2.1–2.5
CEA (ng/mL)	5.25	<3
FBG (mmol/L)	6.0	4.0–5.0

TSH: thyroid stimulating hormone.
CEA: Carcinoembryonic antigen, HDL: high density lipoprotein.

is not totally complemented with supporting literature. This process is known to occur physiologically after a certain age and pathologically in Sjogren's syndrome, alcoholics, diabetics, or patients affected by HIV [1]. In vivo studies conducted on mice show bilateral adipose replacement of the parotid glands several days after ovariectomy. The theory covering this substitution is based on the importance of estrogen on the parotid glands preservation [2]. Other studies on ovariectomized female rats point to specific changes in the synthesis and secretion of proteins by salivary glands, in response to hormonal deficiency. A decline in the amylase activity in the parotid glands, as well as a total decrease of the enzyme activity of the saliva, has been reported [3]. This theory was discarded because the adipose tissue distribution was present not only in the parotid glands, but also in the upper chest and limbs and in the occipital region.

Thymolipomas are a rare pathological disorder, caused by a thymus adipose transformation. These tumours are histologicaly characterized by adipose tissue and thymic remnant tissue, generally with well-delimited formations [4]. This pathology was excluded, as the images did not identify heterogeneous masses and the distribution was not specifically localized in the thymus area. Decrum disease, or adiposis dolorosa/adiposalgia, considered a rare disease, is characterized by obesity and painful lipomatosis distributed in various areas of the body. This pathology is often characterized by psychiatric disorders [5]. Decrum disease was excluded because the adipose tissue accumulated was painless. Angioedema was excluded by virtue of high levels of C1 inhibitor [6].

Final diagnosis

The symmetrically indolent accumulation of adipose tissue, in the neck region and the upper chest (limbs involved), with dysponea, brought us to consider Madelung disease, also called Launois-Bensaude Syndrome [7–9]. Madelung disease has an incidence 1/250,000, is more frequent in males between the ages of 30–60 years, with a higher incidence in alcoholics. However, there are some cases in women who have not abused alcohol [10,11]. This pathology is presented as symmetrical, abnormal, indolent growth of adipose tissue, particularly expressed around the neck, upper limbs and chest. Generally, it is a benign

pathology, whereas malignant degeneration in liposarcoma is very rare [12].

The pathogenesis of this disease is still unknown. The mechanism is thought to include defects in the mitochondrial respiratory chain, deletions and punctiform mutations on mitochondrial DNA, associated with lipolysis and catecholamine-induced lipogenesis alterations. Adipogenesis is thought to be due to an exaggerated hyperplastic proliferation of the subcutaneous brown adipose tissue. The pathogenesis of Madelung disease is mostly characterized by generation of new adipocytes, rather than expansion of existing cells [13].

Two forms of Madelung disease are recognised, based on the distribution of the fat deposits. In the first type the fat deposits appears around the neck, cervical area, shoulders, upper region of the arms and chest, thus giving the patient a 'pseudoathletic' appearance. In the second type the adipose storage extends in the trunk, around the ribs, upper legs, giving this way the patient a generalized obese view [14]. In alcohol abuse induced disease, alcohol abstinence can prevent progression. Surgical interventions such as lipectomy or liposuction, are made in base of the superimposed clinical manifestation or aesthetically [15]. In asymptomatic patients a potential decision is watchful waiting, and in the event of a deterioration, surgical intervention [16]. The potential complication known is the increased angiogenesis and the tendency of masses to encapsulate and invade the surrounding structures. There are few data that indicate a low risk of transformations of lipomas in liposarcomas, based on a mitochondrial DNA mutation. Up to 2012, only two cases had been reported, and there are no cases in which the disease has gone into spontaneous regression [17,18].

Summary

Based on the pathological laboratory manifestation and on the images obtained through CT we conclude that the patient is suffering from Madelung disease. The diagnostic radiography tools can accurately identify the disease and exclude other soft tissue tumors. Since the lipid mass, during hospitalization, did not change and had no complications, the patient will be kept under periodic observation. Should any deterioration take place, surgical intervention will be considered.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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