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Case report

Membranous lipodystrophy
Case report and review of the literature

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Abstract

Membranous lipodystrophy (ML) is a rare hereditary disorder of adipose tissue characterized by polycystic bone lesions and progressive dementia. We describe the case of a 36-year-old woman with mechanical bone pain. Routine laboratory analyses revealed only a type IV hyperlipoproteinemia and hyperexcretion of urinary calcium. Roentgenograms of short and long bones showed symmetrical, well-defined, non-expansile cystic lesions. Bone biopsy found a yellow lipid-like substance in the osteolytic lesions and histopathological studies were non-specific. Neuropsychiatric examination, including cranial computerized tomography (CT), was found to be normal. According to clinical, analytical, radiological and histological findings ML was the diagnosis. No previous cases of ML have been reported in our country as we review the literature concerning this disease.

Keywords: Membranous lipodystrophy; Nasu-Hakola disease; Polycystic lipomembranous osteodysplasia; Presenile dementia

1. Introduction

Membranous lipodystrophy (ML) (or polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy [1] or Nasu-Hakola disease [2]) was first described in 1968 by Jarvi et al. in Finland. ML is a rare disease that affects young adults of either sex, who present with psychiatric symptoms and multiple lytic bone lesions [3]. The pathogenesis and genetic defect of this disease are still unknown. It was first described in 1968 by Jarvi et al. [4] in Finland and was initially given the name "polycystic lipomembranous osteodysplasia combined with progressive dementia". In 1973 it was described by Nasu et al. as a form of regressive degeneration or destruction of the adipose tissue [2].

There are cases reported only in a few countries, mainly in Japan [2,5–7], and sporadic cases in United States [8], Scandinavian countries [1,9–11,17], Italy, England, South Africa, Turkey, France and Belgium [12–16]. An autosomal recessive mode of inheritance has been suggested [10,17,18].

The disease usually affects young adults of either sex, and is characteristic of the presence of multiple lytic bone lesions and progressive dementia whose initial symptoms appear in the fourth or fifth decade of life [3].

In this article we show the first case of ML reported in our country and we review the literature concerning this unusual disease.

2. Case report

A 36-year-old Caucasian woman with a 4-year history of bilateral mechanical knee pain without joint effusion was first seen in our hospital in December 1995. The patient did not have any other symptom. The physical examination did not show any relevant sign. Knee X-ray plains showed symmetrical, well-defined, non-expansile cystic lesions with non-sclerotic margins in the distal ends of the femur and tibia of both knees. An extensive radiologic study was done showing similar symmetric lesions in metaphyseal and epiphyseal

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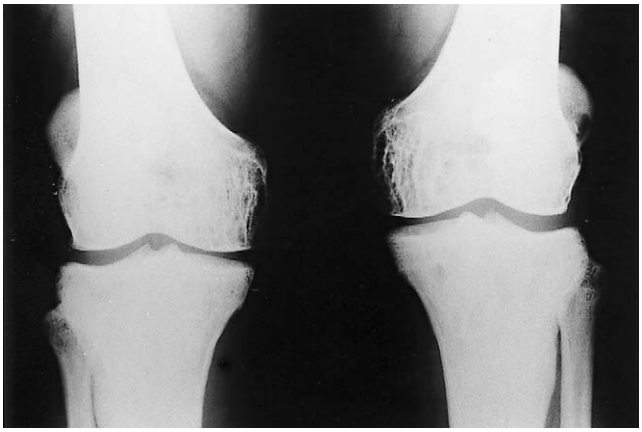

Fig. 1. Roentgenograms of the knees show symmetrical, well-defined, non-expansile cystic lesions in the distal ends of femur and tibia of both knees.

locations of tubular bones of ankles (tibia and fibula), humerus, ulna, radius, carpus, metacarpals and proximal phalanges of hands (Figs. 1–4).

Laboratory tests showed only a type IV hyperlipoproteinemia (with predominance of triglycerides and VLDL)

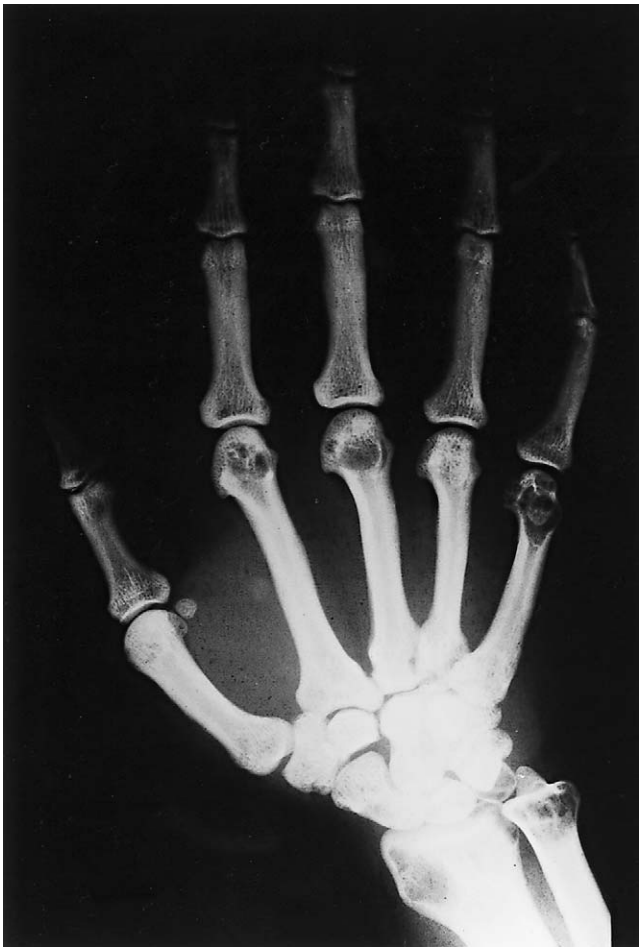

Fig. 2. Roentgenograms of the right hand show the same kind of lytic lesions in the distal ends of radius and ulna, carpal bones, metacarpals and proximal phalanges.

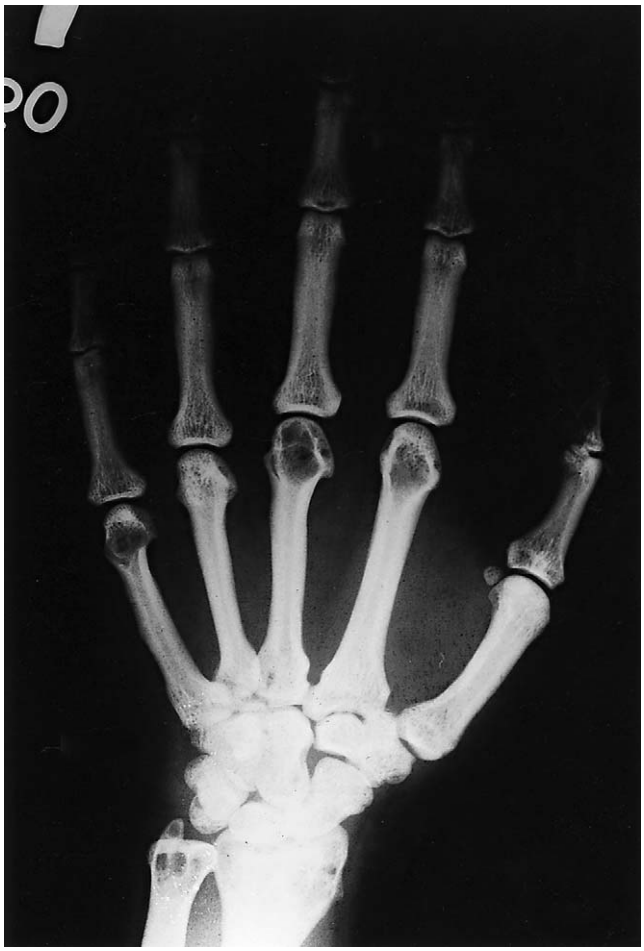

Fig. 3. Roentgenograms of the left hand show the same kind of lytic lesions in the distal ends of radius and ulna, carpal bones, metacarpals and proximal phalanges.

and hyperexcretion of urinary calcium (694 mg in the 24 h collection). Parathyroid and kidney functions were investigated extensively and found to be normal. We did not find any other significant laboratory finding.

Bone densitometry was done by dual X-ray absorptiometry and was found to be normal.

In order to rule out a neoplasia with bone extension an open bone biopsy was obtained from two locations: distal epiphyseal of right femur and distal epiphyseal of right radius. The same findings were seen into the two locations: a gross appearance subcutaneous fat, a very thin and eburneal cortical bone tissue surrounding the osteolytic lesion that contained a yellow lipid-like substance. The histopathological studies showed a cortical bone and endosteal fat tissues of normal characteristics without any infiltrative lesion in both samples (Fig. 5). A normal synovial tissue was found from a sample obtained from the right knee.

Taking all of these radiological, analytical and histopathological features ML was diagnosed. Underlying diseases (including neoplasic disorders, etc.) were ruled out. Abnormalities in brain, kidney and liver have been described in this disorder. For this reason a computerized tomography (CT) was obtained from the cranium without any pathological

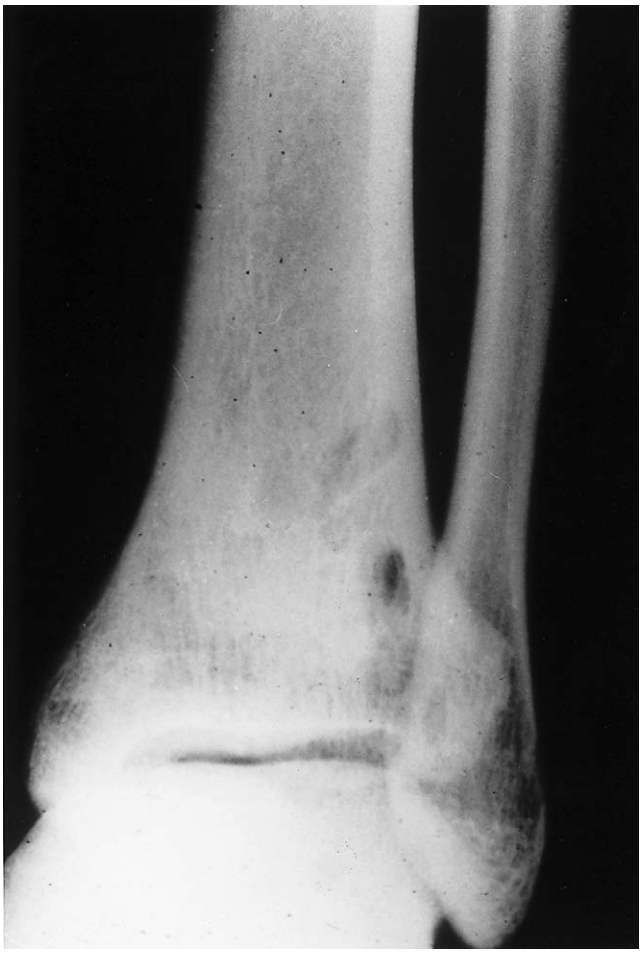

Fig. 4. Roentgenograms of the left ankle show multiloculated lytic lesions in the distal ends of tibia and fibula.

finding, and an abdominal ultrasonography was done that was normal. Neuropsychiatric and neurologic examination revealed no pathologic findings.

It has been suggested that this condition has no effective treatment. However, we started a treatment for the hyperlipoproteinemia and the hypercalciuria with bezafibrato and hydroclorotiazidic diuretic with improvement of triglycerides levels from 551 to 239 mg/dl (normal range in our laboratory from 35 to 165) and the calciuria from 694 mg in 24 h to 274 mg (normal values: 4 mg/kg of body weight; body weight of the patient: 62.9 kg).

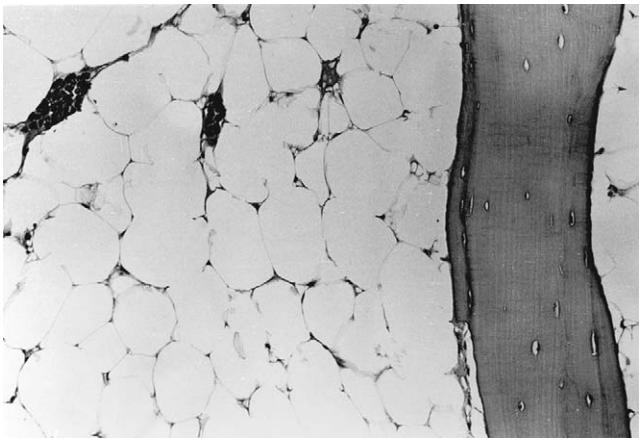

Fig. 5. The histopathological study showed a cortical bone and endosteal fat tissues of normal characteristics without any infiltrative lesion.

After 3 years of follow-up the patient has not developed any neuropsychiatric symptom, any fracture and any other symptom. When the treatment has been stopped the triglycerid level and the calciuria worsened with improvement immediately after restarting the treatment.

3. Discussion

ML is an uncommon disorder that usually appears in young adults of either sex. The initial symptoms arise in the skeleton between the second or third decade of life, with pain, tenderness and fracture after minor injury. Arthritis is not a predominant feature of the disease [3]. In the X-ray examination multiple, multilocular, symmetric and non-expansile cystic characteristic lesions without sclerotic margins can be found in the distal ends of long bones, carpal and tarsal bones, and the short bones of the hands and feet.

Neuropsychiatric symptoms appear later, in the fourth or fifth decade of life, and vary from non-specific symptoms such as memory loss or personality changes to other more important conditions like seizures, decline in mental function and profound dementia, usually in more advanced state of the disease. Patients usually die young, and sometimes the disease resembles Alzheimer's disease [3,18–20]. There appear to be three clinical types of ML: a bone-dominant type, a brain-dominant type and an intermediate one [20]. Our patient could be in the first type.

The neuro-radiologic findings are non-specific and CT shows mild to moderate cerebral cortical atrophy with enlarged lateral ventricles and cerebral sulci. Calcification in the basal ganglia can also be seen. Magnetic resonance (MR) findings in T1-weighted images reveal dilatation of ventricles and cerebral cortical sulci in addition to decreased volume of the cerebral white matter. T2-weighted MR images show a signal intensity of the white matter that is equal to or greater than that of the cortex and a reduced signal density in the putamen and thalamus [21]. There are no prominent patchy or confluent hyperintense areas. It is useful to differentiate between this disease and multi-infarct dementia [20].

There are few comments in the literature of the disease about the analytical abnormalities that can be found in these patients. In the majority of papers, the study was found to be normal. However, a type IV hyperlipoproteinemia has been reported as a characteristic feature of the acquired and congenital lipodystrophies [22].

The pathogenesis of ML is unclear. Some authors believe that the disease is a multisystem genetic disorder of lipid metabolism with autosomal recessive mode of inheritance, but no abnormality of lipid metabolic enzymes has been found [2,5]. Other authors propose that severe chronic vasogenic edema is the main pathogenetic mechanism of severe

leukoencephalopathy development, and that these vascular changes are also present in bone lesions [23].

On the other hand, there are authors who suggest that it represents a metaplastic disorder leading to the replacement of bone for abnormal lipid material [24] and another opinion is that the material is derived from degenerated cells of adjacent stroma [25].

Histopathological ML-like changes are non-specific. A yellow, lipid-like substance is found in the cystic lesions and microscopic examination reveals the tissue to be composed of a lipomatous organization of mature fat cells. The cystic spaces are covered with thick hyaline eosinophilic membranes that are positive for periodic acid-Schiff staining.

For the diagnosis of ML the histopathological study is useful, mainly to exclude neoplasm with bone extension. The ML-like changes found in the osteolytic lesions of these patients are non-specific and these changes of fat tissue have also been found in other diseases [14]. In fact, some authors have established ML diagnosis with unique MR findings, without cystic lesions in bones or histological features [21].

Differential diagnosis of ML is not easy, because these peculiar changes in fat tissue have been associated with other local and systemic diseases including lupus erythematosus, eythema nodosum, fat tissue granuloma, hemodialysis patients with carpal tunnel syndrome, progressive systemic sclerosis, diabetes mellitus, cases of limb ischemic necrosis caused by arteriosclerotic obstruction, thromboamgiitis obliterans, statis dermatitis, etc. [26–31].

Features similar to those found in the osseous tissue have been found in the brain, regarding neuropsychiatric manifestations characteristic of this disease. These cardinal features are the destruction of white matter, loss of both myelin and nerve fibers with intensive reactive gliosis, cortical atrophy and presence of multiple calcifications of the basal ganglia. Some authors proposed that brain and bone lesions may be assumed to share the same pathogenesis [25].

We present in this paper the first case of ML reported in our country. In the few laboratory data described of these patients, we have not found hypercalciuria. This condition could represent the fat metaplastic disorder previously proposed in which normal bone is replaced by lipidic material. In addition, we have not found any specific treatment in the literature of the disease and it has been suggested that this is a fatal illness. However, we have treated and controlled the hyperlipemia and the hypercalciuria. The first could be important in the development of the disease and for this reason its control could delay the development of the fatal neurologic affectation. Moreover, the treatment of the hypercalciuria found in our case, could contribute to delay the development of new osteolytic lesions.

In conclusion, ML is a rare and progressive disease with a possible genetic etiology and with a poor prognosis when it affects the brain. For this, to reach an early diagnosis as well as giving genetic counseling is necessary. It is unknown if the treatment of the metabolic disturbs could delay the fatal evolution to the neurologic disease or if it could prevent bone fractures.

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