CLINICAL ORTHOPAEDICS AND RELATED RESEARCH
Number 454, pp. 262–269

CASE REPORTS

Nasu-Hakola Disease (PLOSL)

Report of Five Cases and Review of the Literature

Henning Madry, MD[*]; Johannes Prudlo, MD[†]; Aleksandr Grgic, MD[‡]; and Jürgen Freyschmidt, MD[§]

The combination of bilateral lytic lesions in the bones of the lower and upper extremities and presenile dementia is characteristic of polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, also known as Nasu-Hakola disease. The clinical course of this rare and fatal disorder is characterized by pathologic fractures of these often painful lesions, rapid progression of dementia, and death in the fifth decade of life. The radiographic changes may be confused with cystic angiomatosis, focal metastasizing hemangioendothelioma, or Langerhans' cell histiocytosis. We report five patients to illustrate the clinical presentation, radiographic images, psychiatric abnormalities, and new genetic findings. Three of the patients were siblings. A biopsy is not needed to confirm the diagnosis of polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy because of the unique combination of radiographic and neurologic features.

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) is characterized by a combination of lytic lesions in the bones of the upper and lower extremities and loss of white matter in the brain leading to presenile dementia.[18] Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy is also known as Nasu-Hakola disease.[11] The lytic lesions occur mainly in the peripheral parts of the lower and upper extremities.[1,4,7,14] In the early stage of the disease, these lesions may undergo pathological fractures.[1,4,14] During the later course, the frontal-type symptoms usually progress rapidly to presenile dementia and eventually death during the fifth decade of life.[17] Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy is a rare hereditary disorder (possibly of autosomal recessive inheritance) with a global distribution.[4,13] Only approximately 200 patients have been diagnosed, most from Finland and Japan, but also from Germany, Brazil, the United States, Italy, France, and South Africa.[12] Although owing to the fractures, orthopaedic surgeons treat most patients with PLOSL, only 10 patients have been reported in the orthopaedic literature.[1,4,7,14]

We describe five additional patients with PLOSL, three of whom were siblings (Table 1). We present these patients to illustrate the clinical course, radiographic findings, psychiatric abnormalities, and underlying genetic abnormalities that may enable orthopaedic surgeons to establish a correct diagnosis during the early stage of the disease to prevent unnecessary biopsies.

Patient 1

A 32-year-old man was admitted to the hospital because of pain in both ankles. The patient was well until 6 months before admission when he felt pain in his right ankle that had increased during the past weeks. Two months before admission, the patient was treated unsuccessfully with

Received: October 17, 2005
Revised: May 23, 2006; July 6, 2006
Accepted: July 14, 2006
From the [*]Department of Orthopaedic Surgery, the [†]Department of Neurology, and the [‡]Department of Nuclear Medicine, Saarland University Medical Center, Homburg/Saar, Germany; and the [§]Department of Radiology, Zentralkrankenhaus, Bremen, Germany.
Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc) that might pose a conflict of interest in connection with the submitted article.
Each author certifies that his or her institution has approved the reporting of this case report, that all investigations were conducted in conformity with ethical principles of research, and that informed consent was obtained.
Correspondence to: Henning Madry, MD, Department of Orthopaedic Surgery, Saarland University Medical Center, Kirrbergerstr. 1, D-66421 Homburg/Saar, Germany. Phone: 49-6841-1624837; Fax: 49-6841-1624988; E-mail: hmad@hotmail.com.
DOI: 10.1097/01.blo.0000229364.57985.df

TABLE 1. Clinical, Neurologic, and Radiographic Findings in the Five Patients with PLOSL

Patient Number	Age at Presentation (years)	Gender	Neurologic Signs at Presentation	Localization	Family History	Pathologic Fracture(s)	Biopsy Performed	Treatment
1	26	Male	Yes	Both tali, right metatarsal	No	Yes (single)	No	Conservative
2	60	Male	No	Right medial and lateral malleolus, right talus, Scaphoid, lunate of both hands	No	No	Yes	Conservative
3	35	Male	Yes	Left fifth metacarpal, right second metatarsal, both second and fifth metatarsal scaphoid, lunate, pisiformis, hamatum, second, fourth, and fifth phalanges	Yes	Yes (multiple)	Yes	Conservative
4	38	Male	No	Right proximal and distal tibia, right talus and ankle, capitatum, scaphoid	Yes	Yes (multiple)	Yes	Conservative (died at 46 years)
5	33	Female	No	Right fifth distal metatarsal, second and fifth middle phalanges of right hand	Yes	Yes (multiple)	No	Conservative

PLOSL = polycystic lipomembranous osteodysplasia with sclerosing leukonencephalopathy

nonsteroidal antiinflammatory agents (NSAIDs). The pain was characterized as dull and being present day and night. His medical history was unremarkable. There was no history of previous accidents, surgeries, or sport activities. The family history was uneventful, and there were no known Scandinavian or Japanese ancestors. His history revealed that when he was 25 years old, he had neuropsychiatric symptoms develop starting with erectile dysfunction which was treated with sildenafil. From 30 years onward the patient had early clinical signs of a frontal dementia with social and affective inappropriateness, disinhibition, and loss of insight into the extent of the disorder.

There was no rash or skin lesions, and his ankles were not warmer than other parts of the lower extremities. There was diffuse tenderness over the anterior parts of both tali. The patient's neurologic examination was normal with the exception of subtle eye movement abnormalities in the form of saccadic dysmetria. Laboratory tests were unremarkable. Anteroposterior (AP) and lateral radiographs of both ankles showed several bilateral, geographic lytic lesions in both tali which were partially surrounded by sclerotic rims (Fig 1A). These lesions occupied almost all of the talus. There was no endosteal scalloping, cortical destruction, or periosteal reactions. Computed tomography (CT) revealed smooth, marginated cystic lesions in both tali and minute cystic lesions in the metatarsal bones (Fig 1B). Radiographs of both wrists revealed bilateral, lytic lesions in both scaphoids. A radionuclide bone scan showed increased uptake in the right talus and less extensive uptake in the left talus and distal second right metatarsal bone. An abdominal ultrasound was normal. Magnetic resonance imaging (MRI) revealed the content of the lytic lesions was fat-equivalent (Fig 1C–D).

The patient received NSAIDs for musculoskeletal problems and was discharged on crutches. Two months later, the patient was admitted to the hospital emergency room after he had fallen into a 1.5-m deep construction hole. On examination the right ankle was tender and swollen. Anteroposterior and lateral radiographs of the ankle revealed a pathologic compression fracture through the talus with severe impaction at the fracture site. The fracture was treated by immobilization in a short leg cast for 12 weeks. Four years later he walks without crutches. The range of motion (ROM) of his upper ankle joint is normal and his ankles are not painful. The extent of cognitive impairment increased. The patient exhibits increasing forgetfulness, emotional blunting, and a decline in interpersonal conduct.

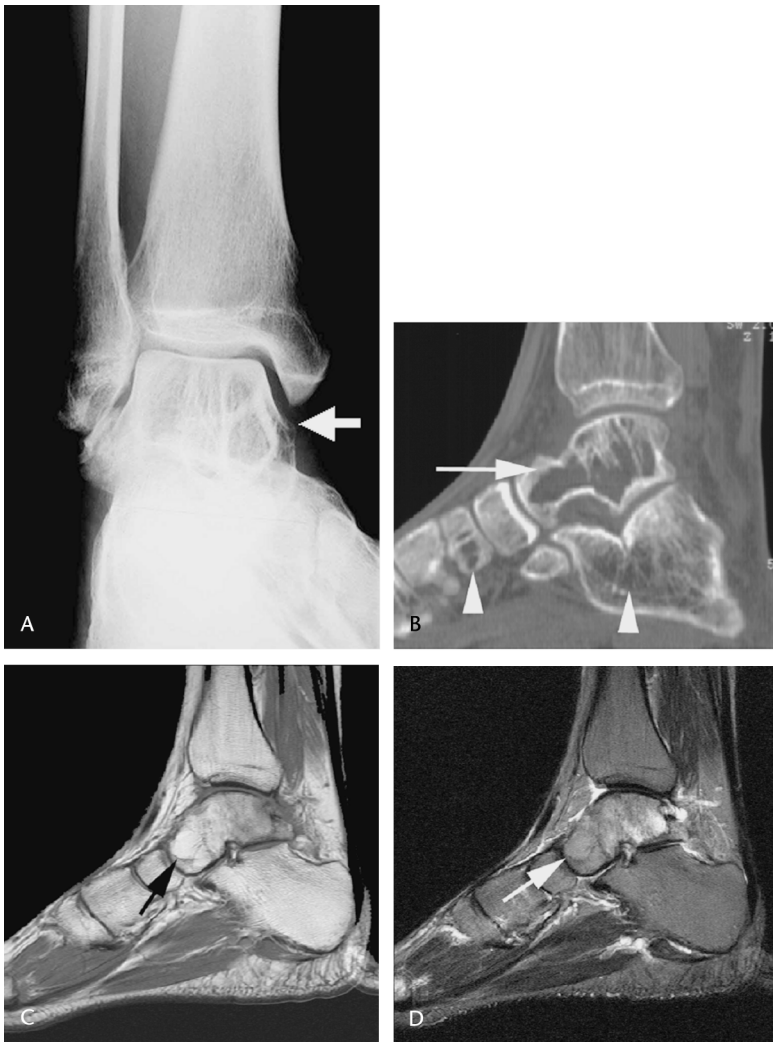

Fig 1A–D. (A) An AP radiograph of the right ankle shows a smooth, loculated, marginated lesion with loss of trabeculation and sclerosis surrounding the rim in the talar dome (arrow). (B) A CT scan shows the extension of the geographic lesions (arrows) occupying both tali with preservation of the cortical margins, and no definite soft tissue component. There is no endosteal scalloping or periosteal lamellar reaction. Minute lesions are present in the calcaneus and in the middle foot (arrowheads). A T1-weighted MR image of the right ankle at approximately the same level as the CT scan shows increased signal intensity. (D) The TIRM (Turbo-Inversion Recovery-Magnitude) image shows loss of signal intensity, indicating a substantial amount of fat in the lesion.

Patient 2

A 60-year-old man was admitted to the hospital because of pain in his right ankle. The pain initially appeared after a longer hiking trip but did not diminish for months. The patient did not show any neurologic abnormalities. His family history was otherwise unremarkable. Anteroposterior and lateral radiographs of his right ankle showed large lytic lesions in the malleolus lateralis and in the malleolus medialis, both extending into the epiphyseal parts of the distal fibula and tibia and the corpus and collum tali. Similar lesions also were present in the scaphoid and the lunate of both hands (Fig 2). A radionuclide bone scan showed enhanced tracer uptake corresponding to these areas. Magnetic resonance imaging and CT of the osteolytic lesions revealed a content that was fat-equivalent. Cranial MRI revealed no abnormalities. An incisional biopsy was performed at the right lateral malleolus. Fatty tissue was found in the lytic lesions, which was separated by folded membranes that stained positive for periodic acid-Schiff (PAS). The patient was diagnosed with lipomembranous osteodysplasia after histopathologic examination. Currently, the patient is without any neurologic signs.

Patient 3

A 35-year-old man was admitted to the hospital because of pain in his right foot for 4 weeks. Two years earlier he began experiencing difficulty concentrating. At the same time, his wife noticed a change in his personality. His medical history was uneventful. Physical examination revealed tenderness over the heads of his left fifth metacarpal and right second metatarsal. Plain radiographs showed pathologic fractures through the lytic lesion in his left fifth metacarpal and right second metatarsal that were partially surrounded by sclerotic rims (Fig 3A). Similar lesions

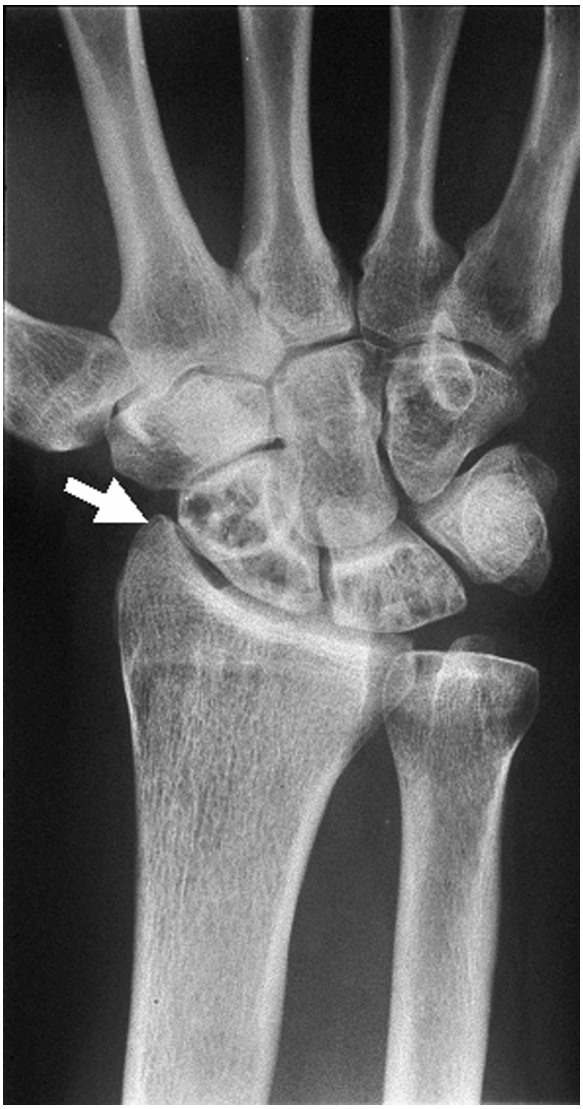

Fig 2. An AP radiograph of the wrist shows a radiolucent, loculated, smooth marginated lesion in the scaphoid (arrow) and in the lunate surrounded by sclerotic rims.

were found in the heads of the second and fifth metatarsals of both legs. The scaphoid, lunate, pisiform, and hamate were involved in the left hand. Several small lytic lesions were seen in the distal metaphyseal parts of the proximal second, fourth, and fifth phalanges. A neurologic examination revealed bilateral pyramidal signs and discrete electrophysiologic changes. There was some ataxia indicated by the Romberg test and a slowly progressive spastic-atactic change in gait. Magnetic resonance imaging of the brain showed a leukodystrophic process. We then performed an open biopsy at the site of the pathologic fracture of the second right metatarsal. Histopathologic analysis revealed undulating membranes in the bone marrow (which was altered to a fatty appearance) that were PAS-positive (Fig 3B). The patient became increasingly demented during hospitalization. He was discharged in a wheelchair that he still needs 8 years later.

Patient 4

The 38-year-old brother of Patients 3 and 5 initially was admitted to the hospital because of pain in his left ankle and right knee. The pain was dull and persisted for years. He recalled pain in his ankles since he was in his early twenties. At 22 years, he sustained a pathologic fracture of his left ankle, which was treated nonoperatively. At that time he was diagnosed with a cystic bone angiomatosis. He took NSAIDs and has walked using crutches for the last few years. His medical history was otherwise unremarkable. Physical examination revealed tenderness over his left ankle and proximal tibia. Anteroposterior and lateral radiographs revealed a lytic process in his right proximal lateral tibial epiphysis (Fig 4). There were multiple lytic lesions in his distal tibia, talus, ankle, and signs of osteoarthritis (OA) in his upper ankle. The joint space was not significantly narrowed, but there were signs of subchondral sclerosis and some osteophytes. Radiographs of his hands revealed lytic structures in his capitate and scaphoid. An open biopsy of the tibial lesion was performed. Microscopic evaluation of the tissue showed little trabecular and cortical bone, which was remarkably thin. There were convoluted membranes that formed cystic structures. The patient was treated nonoperatively and discharged. During the next few years he experienced multiple pathologic fractures of his femurs, tibiae, pelvis, and spine. He also had progressive loss of concentration as documented by personal correspondence and a progredient dementia with atactic movements. These neurologic symptoms were accompanied by upper motor neuron signs. The patient died at 46 years of pneumonia and in a mute state.

Patient 5

When the 45-year-old sister of the two brothers (Patients 3 and 4) initially was seen at the age of 33, she had no clinical signs of PLOSL. At this time, radiographs were obtained because her brothers were diagnosed with PLOSL and a family history was sought. Anteroposterior and lateral radiographs of her right hand and foot revealed lytic lesions in the fifth distal metatarsal and in the second and fifth distal middle phalanges of her hand (Fig 5). After 12 years of followup, at the age of 45 years, she had neuropsychiatric signs of PLOSL develop. The skeletal lesions were progressing and led to multiple pathologic fractures that were treated nonoperatively. This information was received from her relatives.

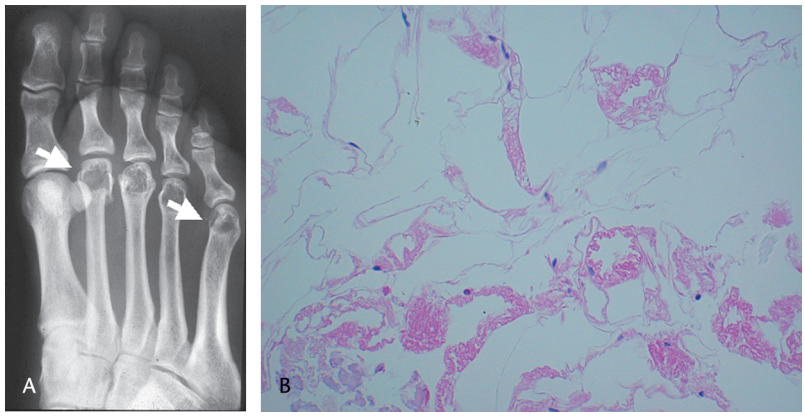

Fig 3A–B. (A) An AP radiograph of the right foot shows radiolucent lesions in the second and fifth metatarsal heads. There is discontinuity of the cortex of the second metatarsal, representing a pathologic fracture. (B) Histopathologic analysis of the tissue retrieved from the site of the pathologic fracture of the second right metatarsal revealed dystrophic lipocytes with the diagnostic PAS-positive membranes in the bone marrow, exhibiting the very characteristic wrinkled appearance.

DISCUSSION

The first patients with PLOSL were described by Terayama in 1961 as a lytic bone disease with peculiar features.[18] In 1973, it was described as a new entity by Nasu et al.[11] Hakola suggested the name lipomembranous polycystic osteodysplasia in 1972.[2] We observed five patients with PLOSL (Table 1); three were siblings. Their parents were nonconsanguinous without signs of the disease. The two other patients had an unremarkable family history. At the time of the initial presentation, four patients had pain in the affected bones and two experienced spontaneous fractures. The specific history regarding the bony lesions ranged from a few months to as much as 10 years. Only one patient had neuropsychiatric symptoms at the first presentation, but all patients had frontal lobe symptoms and presenile dementia develop during the 10-year followup in their fourth and fifth decades of life. Only Patient one in our series initially was diagnosed with PLOSL because of the presence of bilateral lytic lesions in the talar bones and striking neuropsychiatric abnormalities at his first presentation. Although biopsies were performed in Patients 2, 3, and 4, they generally were not necessary to confirm the diagnosis of PLOSL.

The typical radiographic findings in the early stages are a general reduction of the trabeculae in the epiphyses and metaphyses of the long bones.[1,7] Subsequently, a total loss of bone occurs in the affected areas with the formation of pseudocystic lesions, typically in the distal small bones of the extremities and the long tubular bones. Lytic lesions and trabecular loss are most conspicuous in the fingers and in the carpal and tarsal bones. The main radiographic signs include bilateral, geographic polyostotic lytic lesions that in some cases are surrounded by solid sclerotic rims, but in other cases are ill-defined. These lesions may occupy almost all of the volume of the affected bone. The radiographic differential diagnosis includes cystic hemangiomatosis, focal metastasizing hemangioendothelioma, and Langerhans cell histiocytosis. In the case of cystic hemangiomatosis, multiple unilateral or bilateral metaphyseal lesions with diameters of several centimeters may occur. The usually have endosteal thickening.[8,9] In cystic hemangiomatosis, the osteolytic lesions may symmetrically affect the lower extremity.[8,9] Metastasizing hemangioendothelioma is usually asymmetrically distributed.[5] Langerhans cell histiocytosis occurs mostly diaphyseal; however, epiphyseal also lesions have been described.[16] The lesions may show lytic expansile pattern with sometimes ill-defined and sometimes sclerotic margins.[8,9] Nuclear bone scans show a symmetric uptake in involved areas of the appendicular skeleton.[3] The main criteria for the differential diagnosis are the attenuation values by CT and the increased signal intensities on T1-weighted MR images of the lesions. If these values are fat-equivalent, cystic hemangiomatosis or focal metastasizing hemangioendothelioma can be ruled out. Another important differential diagnosis includes sarcoidosis in the hand (also termed ostitis lytica multiplex). However, usually more pathognomonic signs are present in hands and feet with sarcoidosis such as periosteal reactions and akroosteolyses.[15] A chest radiograph usually can exclude this diagnosis. A rare differential diagnosis includes malignant nonHodgkin's lymphomas, in particular the lymphoplasmacytoid type with plasmoplastic dedifferentiation.[19] However, with CT the affected tissue has attenuation values equal to those of nonfatty structures. In addition, neurologic symptoms usually are absent in patients with these differential diagnoses.[10]

Neurologic symptoms of PLOSL include psychotic periods, loss of social inhibitions, euphoria, progressive dementia, myoclonic twitches, convulsions, gait disturbance, and primitive reflexes that ultimately lead to premature death.[2,12,17] They are based on myelin loss, astrocytic gliosis, calcifications, and atrophy of basal ganglia and atrophy of corpus callosum.[2,12,17] The neurologic diagnosis usually is established in the second and third decades of

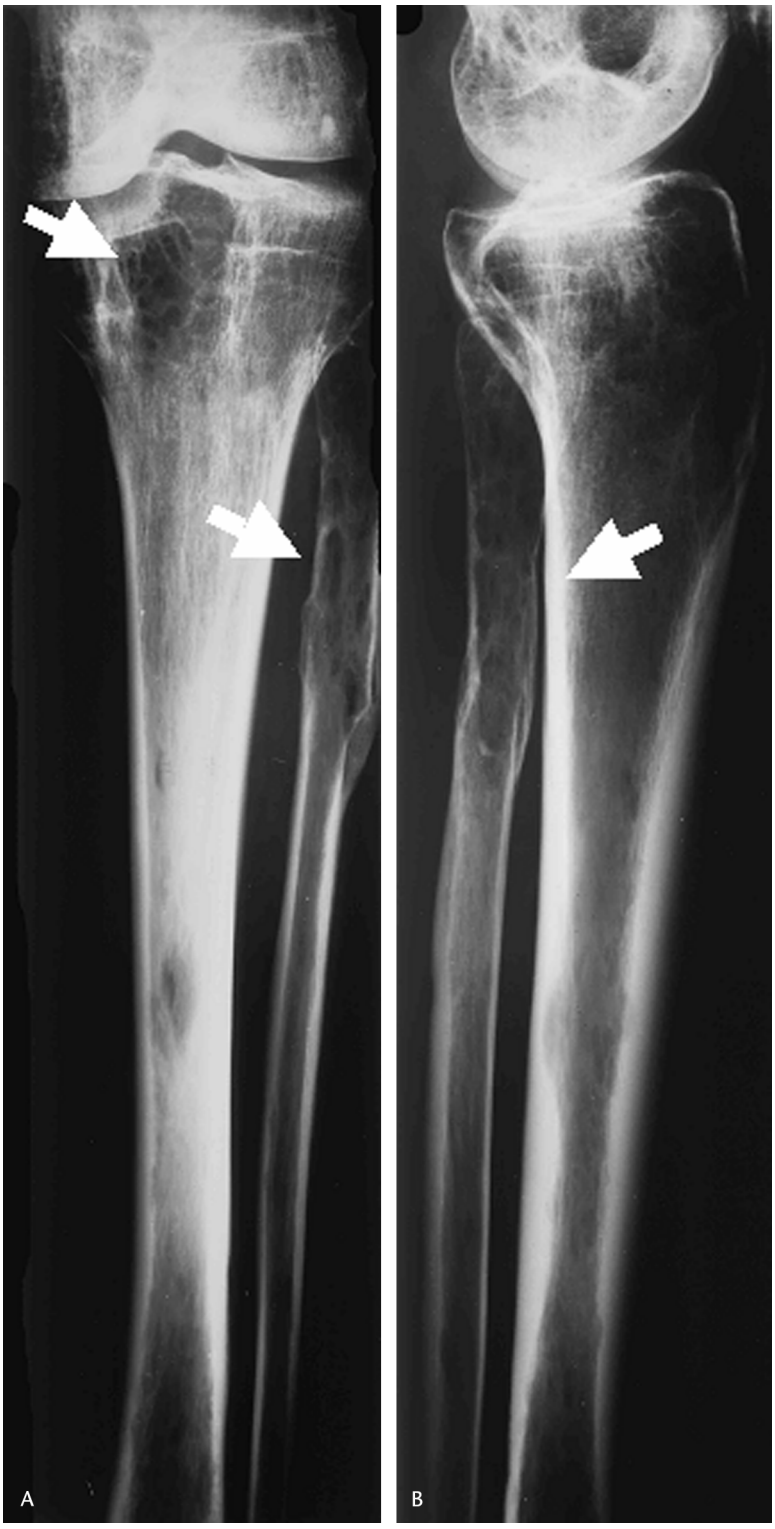

Fig 4A–B. (A) Anteroposterior and (B) lateral radiographs of the left lower leg show the confluent radiolucent lesions in the proximal fibula and tibia. There are also minute radiolucent lesions in the diaphysis of the left tibia.

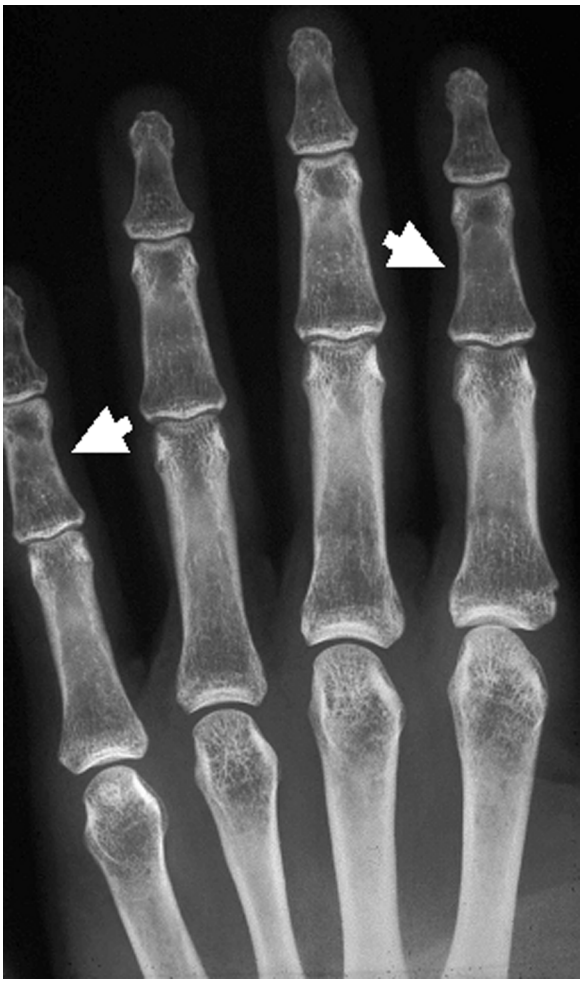

Fig 5. An AP radiograph of the right hand shows small, well-marginated radiolucent lesions in the second and fifth middle phalanges (arrows).

life.[2,12,17] In later stages the patients exhibit a progressive dementia and a vegetative state which, during the course of several years, leads to death during mid-adult life.[6] Laboratory parameters are usually unremarkable.

The pathogenesis of PLOSL is unknown.[6] A genetic background for PLOSL has been suggested.[4,13] Molecular defects based on mutations in two genes, TYROBP (formerly DAP12) and TREM2 were characterized by Paloneva et al.[13] DAP12 is a transmembrane adaptor protein that associates with the cell surface receptor, TREM2.[13] The TYROBP–TREM2 complex is involved in the maturation of dendritic cells. The mutations in TYROBP and TREM2 result in inefficient and delayed differentiation of osteoclasts with reduced bone-remodeling capability. The expression of TYROPB in the monocyte/macrophage lineage may provide an explanation for the unique combination of skeletal lesions and neurologic symptoms. Osteoclasts and microglial cells in the central nervous system are phagocytic cells of hematopoietic origin and share a common differentiation pathway.[13] Bone pseudocysts may result from chronic dysfunction of osteoclasts, leading to a defective bone remodeling.[13] The changes in the central nervous system may arise from the inability of microglial cells to remove apoptotic tissue in the brain, leading to sclerosing leukoencephalopathy. Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy is not a lipid storage disease, as the analysis of lipid or lysosomal enzyme activities is normal. However, despite the primary cause of PLOSL, the molecular and cellular pathogeneses of the disease remain unknown. Because of this unknown etiology, treatment of PLOSL is symptomatic. Pathologic fractures usually are treated nonoperatively.

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy should be considered when bilateral osteolytic lesions are seen on radiographs of the lower and upper peripheral appendicular skeleton in patients approximately 30 years of age who have early signs of dementia. These lesions are often painful, and pathologic fractures are common. The key to the radiographic diagnosis is the fat-equivalent content of the lesions on MRI or CT. A biopsy generally is not needed because of the classic combination of these particular radiographic and neurologic findings. The rarity of PLOSL makes it difficult to study, and additional genetic investigations are necessary to determine a targeted therapy.

Acknowledgments

We thank Helmut Ostertag, MD, for providing the histopathologic picture (Patient 3) and Dieter Kohn, MD, for helpful suggestions.

References

1. Akai M, Tateishi A, Cheng CH. Morii K, Abe M, Ohno T, Ben M. Membranous lipodystrophy: a clinicopathological study of six cases. *J Bone Joint Surg Am*. 1977;59:802–809.
2. Hakola HP. Neuropsychiatric and genetic aspects of a new hereditary disease characterized by progressive dementia and lipomembranous polycystic osteodysplasia. *Acta Psychiatr Scand Suppl*. 1972;232:1–173.
3. Hakola HP, Karjalainen P, Virtama P. Bone scintigraphy in polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy. *Nucl Med Commun*. 1988;9:1005–1011.
4. Hasegawa Y, Inagaki Y. Membranous lipodystrophy (lipomembranous polycystic osteodysplasia): two case reports. *Clin Orthop Relat Res*. 1983;181:229–232.
5. Kleer CG, Unni KK, McLeod RA. Epithelioid hemangioendothelioma of bone. *Am J Surg Pathol*. 1996;20:1301–1311.
6. Klunemann HH, Ridha BH, Magy L. Wherrett JR, Hemelsoet DM, Keen RW, De Bleecker JL, Rossor MN, Marienhagen J, Klein HE, Peltonen L, Paloneva J. The genetic causes of basal ganglia calcification, dementia, and bone cysts: DAP12 and TREM2. *Neurology*. 2005;64:1502–1507.
7. Kocer N, Dervisoglu S, Ersavasti G, Altug A, Cokyuksel O. Case

report 867: membranous lipodystrophy (polycystic lipomembranous osteodysplasia). *Skeletal Radiol*. 1994;23:577–579.
8. Lateur L, Simoens CJ, Gryspeerdt S, Samson I, Mertens V, Van Damme B. Skeletal cystic angiomatosis. *Skeletal Radiol*. 1996;25: 92–95.
9. Levey DS, MacCormack LM, Sartoris DJ, Haghighi P, Resnick D, Thorne R. Cystic angiomatosis: case report and review of the literature. *Skeletal Radiol*. 1996;25:287–293.
10. Mulligan ME. Myeloma and lymphoma. *Semin Musculoskelet Radiol*. 2000;4:127–135.
11. Nasu T, Tsukahara Y, Terayama K. A lipid metabolic disease-"membranous lipodystrophy"-an autopsy case demonstrating numerous peculiar membrane-structures composed of compound lipid in bone and bone marrow and various adipose tissues. *Acta Pathol Jpn*. 1973;23:539–558.
12. Paloneva J, Autti T, Raininko R. Partanen J, Salonen O, Puranen M, Hakola P, Haltia M. CNS manifestations of Nasu-Hakola disease: a frontal dementia with bone cysts. *Neurology*. 2001;56:1552–1558.
13. Paloneva J, Kestila M, Wu J, Salminen A, Bohling T, Ruotsalainen V, Hakola P, Bakker AB, Phillips JH, Pekkarinen P, Lanier LL, Timonen T, Peltonen L. Loss-of-function mutations in TYROBP (DAP12) result in a presenile dementia with bone cysts. *Nat Genet*. 2000;25:357–361.
14. Sami S, Liu G, Hornicek F, Cates JM, Mankin HJ. Membranous lipodystrophy: a case report. *J Bone Joint Surg Am*. 2002;84: 630–633.
15. Sartoris DJ, Resnick D, Resnik C, Yaghmai I. Musculoskeletal manifestations of sarcoidosis. *Semin Roentgenol*. 1985;20:376–386.
16. Stull MA, Kransdorf MJ, Devaney KO. Langerhans cell histiocytosis of bone. *Radiographics*. 1992;12:801–823.
17. Tanaka J. Nasu-Hakola disease: a review of its leukoencephalopathic and membranolipodystrophic features. *Neuropathology*. 2000;20:S25–S29.
18. Terayama K. Two cases of cystic bone disease with peculiar features. *J Jpn Orthop Assoc*. 1961;35:626.
19. Vermess M, Pearson KD, Einstein AB, Fahey JL. Osseous manifestations of Waldenstrom's macroglobulinemia. *Radiology*. 1972; 102:497–504.