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Type I Gaucher disease: extraosseous extension of skeletal disease

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Abstract *Objective.* To investigate the frequency and morphology of extraosseous extension in patients with Gaucher disease type I.

Design and patients. MRI examinations of the lower extremities were analyzed in 70 patients with Gaucher disease type I. Additionally, the thoracic spine and the midface were investigated on MRI in two patients.

Results. Four cases are presented in which patients with Gaucher disease type I and severe skeletal involvement developed destruction or protrusion of the cortex with extraosseous extension into soft tissues. In one patient, Gaucher cell deposits destroyed the cortex of the mandible and extended into the masseter muscle. In the second patient, multiple paravertebral masses with localized destruction of the cortex were apparent in the thoracic spine. In the third and fourth patient, cortical destruction with extraosseous tissue extending into soft tissues was seen in the lower limbs.

Conclusions. Extraosseous extension is a rare manifestation of Gaucher bone disease. While an increased risk of cancer, especially hematopoietic in origin, is known in patients with Gaucher disease, these extraosseous benign manifestations that may mimic malignant processes should be considered in the differential diagnosis of extraosseous extension into soft tissues. A narrow neck of tissue was apparent in all cases connecting bone and extraosseous extensions.

Key words Gaucher disease · Bone disease · Extraosseous Gaucher disease · Bone marrow imaging · MRI

Introduction

Gaucher disease is an inborn error of glycosphingolipid metabolism and is the most frequent lysosomal storage disorder [1]. It is caused by an insufficiency of glucocerebrosidase (glucosylceramidase) activity with secondary accumulation of glucocerebrosides within the lysosomes of macrophages [2, 3]. The storage disorder produces a multisystem disease characterized by progressive visceral enlargement and gradual replacement of bone marrow with lipid-laden macrophages. Symptomatic anemia, coagulation abnormalities, hepatosplenomegaly and structural skeletal changes occur at some point during the course of illness in most patients.

Skeletal involvement is a major cause of morbidity, afflicting up to 75% of patients, but varies widely between and within individual patients. Bone lesions range from mild osteopenia, medullary expansion and remodeling defects (e.g., Erlenmeyer flask deformity) to osteonecrosis of the femoral or humeral heads and spinal cord compression from vertebral collapse [4, 5]. Extraosseous manifestation of Gaucher disease is supposed to be extremely rare [6, 7]. We report four patients with Gaucher disease type I demonstrating extraosseous extension or medullary expansion with protrusion of the cortex.

Since 1991, patients with Gaucher disease type I have been examined clinically and radiologically by an interdisciplinary study group. MRI of the lower extremities in

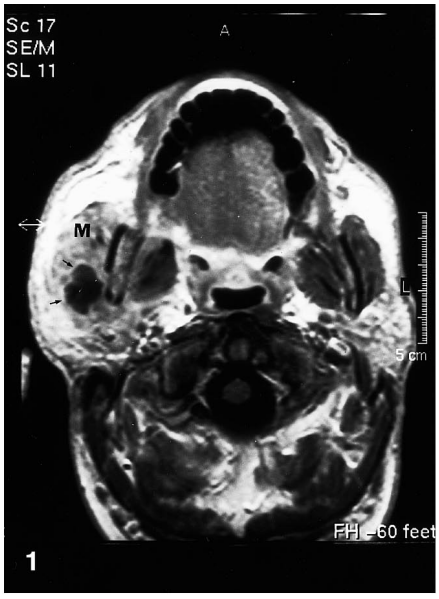


Fig. 1 Case 1. T1-weighted axial spin-echo image of the midface after gadolinium enhancement (TR/TE: 625/25 ms; slice thickness 5 mm) shows a low signal intensity mass in the right masseter muscle with a contrast-enhancing capsule (*black arrows*). *M* right masseter muscle

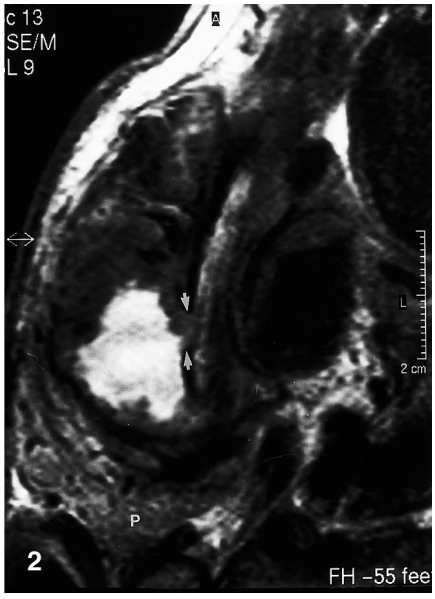
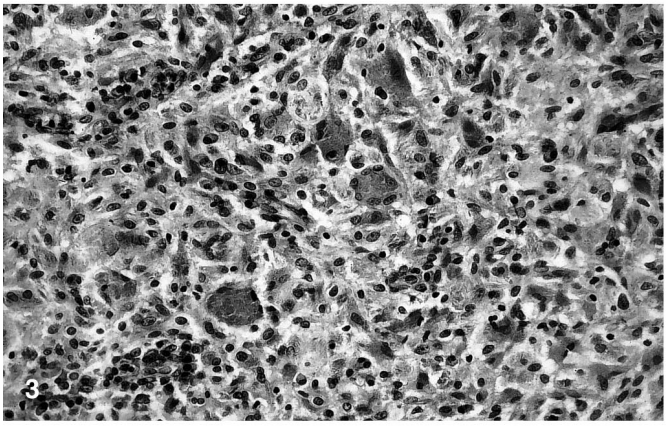
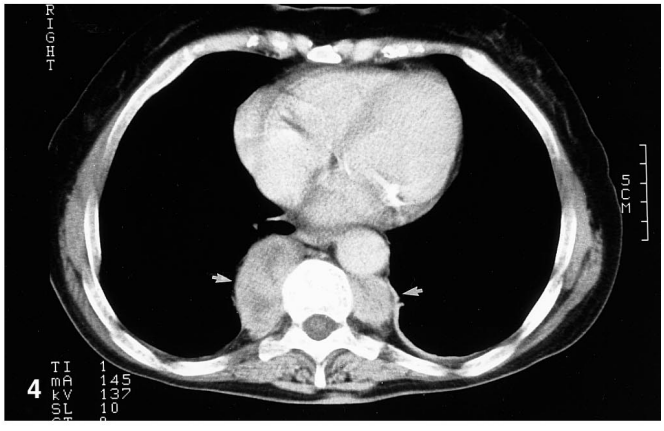


Fig. 2 Case 1. On T2-weighted axial turbo-spin-echo (TSE) image of the right midface (TR/TE: 2200/100 ms; slice thickness 3 mm) Gaucher cell extension appears hyperintense, indicating fluid or proteinaceous content within the mass. Note the narrow neck of tissue between the lateral cortical mandible and the tumor (*white arrows*). *P* right parotid gland





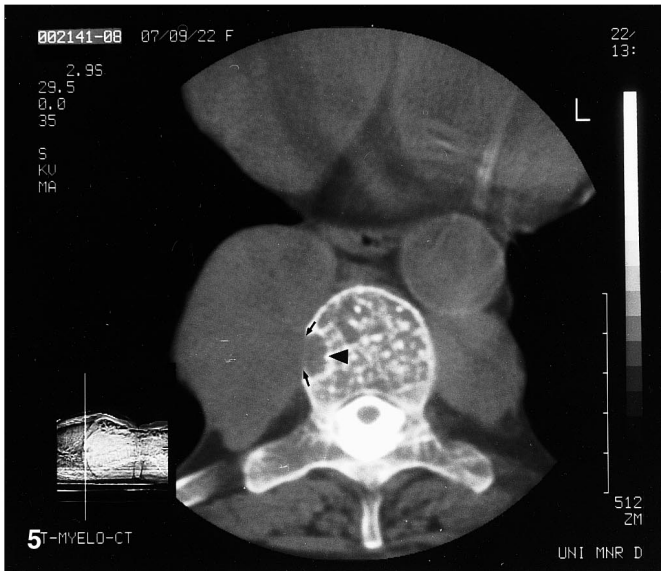


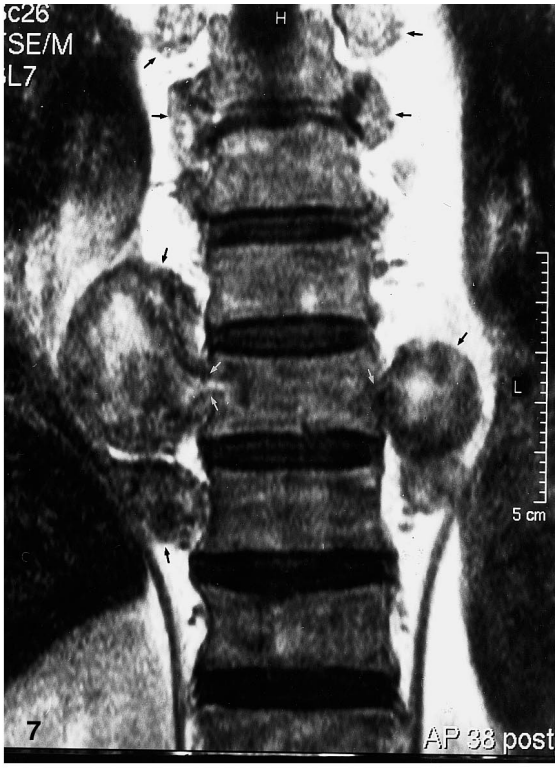
Fig. 3 Case 1. High-power photomicrograph of the extraosseous soft tissue mass with accumulation of glucocerebroside-laden histiocytes and plasma cell infiltrates. (PAS, original magnification ×870)

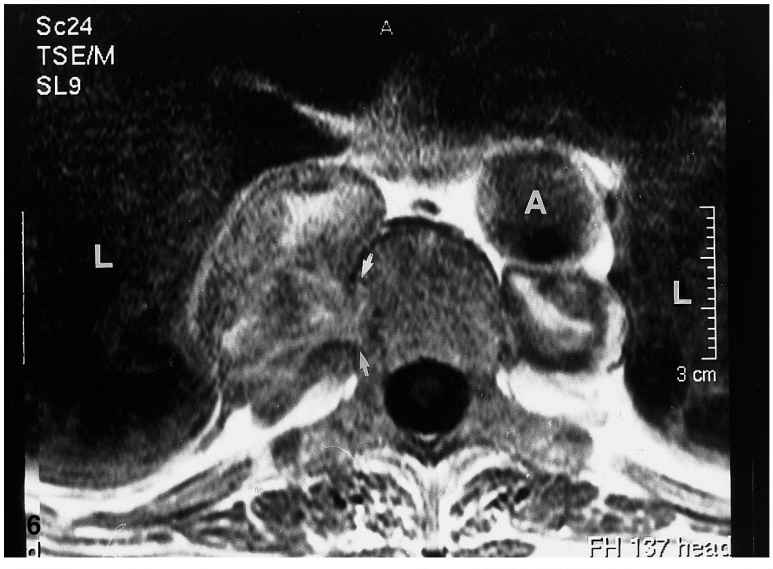
Fig. 4 Case 2. Contrast-enhanced CT scan of the chest demonstrates paravertebral masses with homogeneous, strong contrast enhancement (*white arrows*)

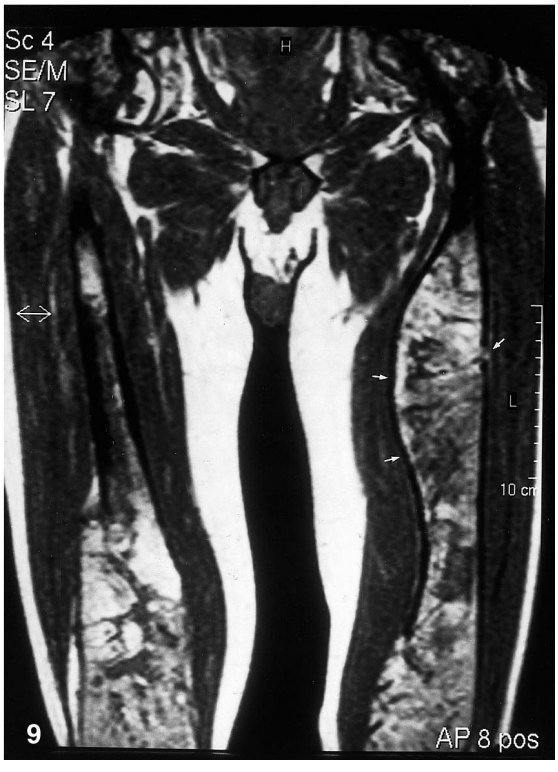
Fig. 5 Case 2. Post-myelography CT scan shows an osteolytic lesion within a thoracic vertebral body (*black arrowhead*) and a lytic intracortical lesion (*small black arrows*)

Fig. 6 Case 2. T1-weighted TSE image in the axial plane (TR/TE: 625/25 ms; slice thickness 3 mm) reveals paravertebral masses with a comparable signal intensity to the vertebral body. Note the neck of tissue (*white arrows*) between vertebral body and mass. The right paravertebral mass impresses the right pleura and lung; the left mass reaches the pleural surface. Areas of high signal intensity within the masses indicate areas of fatty degeneration. The vertebral body appears with decreased signal intensity due to intramedullary Gaucher cell deposits. *L* lungs, *A* aorta

Fig. 7 Case 2. T1-weighted TSE image in the coronal plane (TR/TE: 625/25 ms) with multiple paravertebral masses (*small black arrows*). Note the conjunction (*small white arrows*) between the vertebral body and paravertebral masses. Diffuse abnormal low signal intensity of the thoracic spine indicates a reduction in fat marrow by Gaucher cell deposits







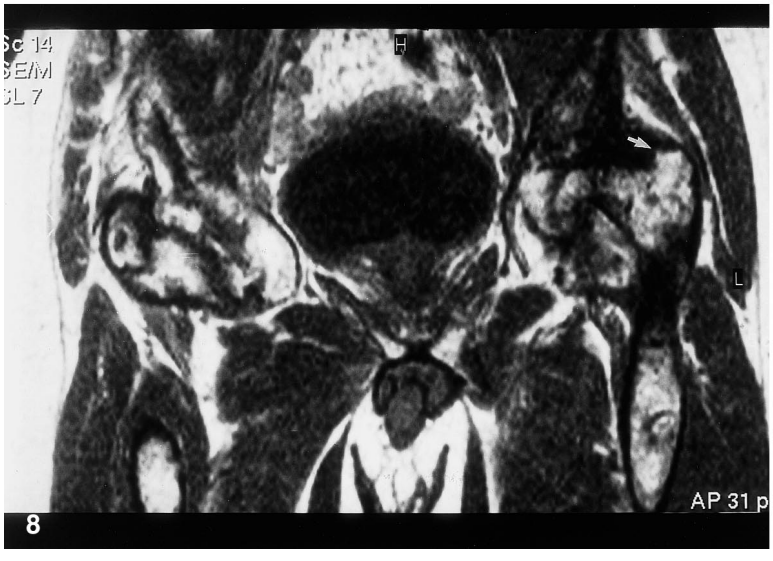


Fig. 8 Case 3. T1-weighted image in the coronal plane (TR/TE: 615/25 ms) reveals severe osteoarthrosis in both hips with extensive deformities of the femoral heads. Extraosseous extension is seen on the craniolateral aspect of the left greater trochanter (*white arrow*)

Fig. 9 Case 3. T1-weighted SE image in the coronal plane (TR/TE: 615/25 ms; slice thickness 4 mm) of the thighs demonstrating inhomogeneous decreased signal intensity in both femora. Note the flask deformity of the left femoral diaphysis (*white arrows*), a small cortical protrusion of the lateral femoral diaphysis (*white arrow*) and a consolidated pathological fracture of the right distal femur

70 patients with Gaucher disease type I was performed. Some of these patients received additional MR scans at anatomical sites other than the lower extremities depending on their clinical presentation [8].

Case reports

Case 1

A 47-year-old-man was admitted for investigation of a painful swelling of the right oral vestibulum and hypoaesthesia of the right mental nerve. Gaucher disease had been diagnosed in 1971 by bone marrow and liver biopsy; the genotype was L444P/L444P. At the age of 33 years splenectomy was performed for excessive splenomegaly, following which the general condition deteriorated with fatigue and disabling bone pain. Enzyme replacement therapy was initiated in 1995, due to severe skeletal involvement as demonstrated by MRI of the lower extremities. Imiglucerase (Cerezyme; Genzyme, Cambridge, Mass.) was administered intravenously every 2 weeks at a dose of 60 IU /kg body weight.

In January 1999, a submucosal dentogenic abscess was drained and premolars and molars of the right mandible extracted. An orthopantomogram showed generalized osteopenia of the right mandible, and radiolucencies of the right premolar and molar region.

Two months later, the patient complained of severe pain in the right buccal area and physical examination showed a fluctuating swelling in the right masseter muscle. The radiolucencies of the right premolar and molar region had progressed and MRI of the right midface showed a well-circumscribed mass within the right masseter muscle, appearing hypointense with a contrast-enhancing capsule on T1-weighted images (Fig. 1) and hyperintense on T2-weighted images, indicating fluid within the mass (Fig. 2). Destruction of the lateral cortex of the mandible was seen with a continuity of mandible tissue and the mass (Figs. 1, 2). Histopathological analysis revealed accumulations of Gaucher cells with lymphoid plasma cell infiltration (Fig. 3). The buccal swelling resolved after drainage and administration of intravenous antibiotics.

Case 2

A 76-year-old woman was diagnosed with Gaucher disease type I at the age of 45 years by bone marrow biopsy. Glucocerebrosidase activity in peripheral blood leukocytes was decreased. At the age of 69 years she had undergone total hip replacement following a pathological fracture of the left femoral neck. In her past medical history fractures of the malleolus, humerus, and lower leg had occurred. In 1996, at 74 years, she presented with

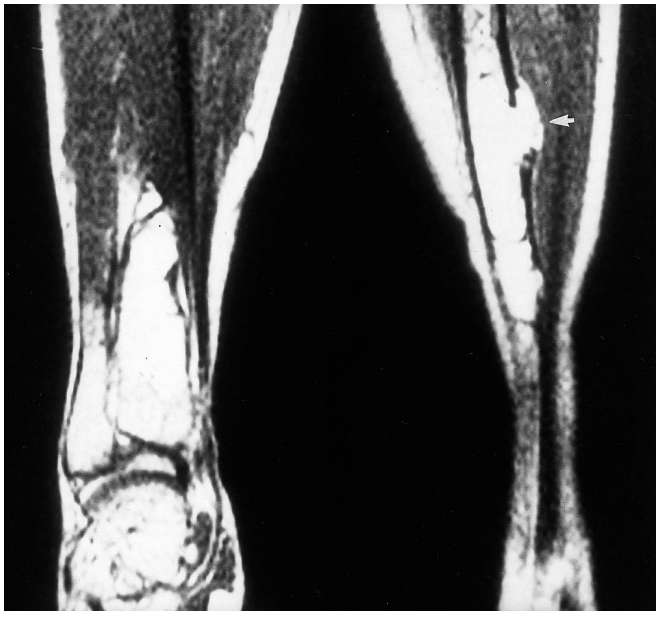


Fig. 10 Case 3. T1-weighted image in the coronal plane (slice thickness 5 mm) of the lower limbs shows cortical extension into soft tissue in the lateral aspect of the left tibial diaphysis (*white arrow*)

anemia, thrombocytopenia, and splenomegaly with extensive skeletal involvement, demonstrated by MRI of the lower extremities. A contrast-enhanced CT scan of the chest revealed multiple enhancing paravertebral masses in the middle and lower thoracic spine (Fig. 4). Conventional myelography showed no intracanal abnormality but the post-myelography CT scan of the thoracic spine showed localized destruction of the right lateral cortex and an additional osteolytic lesion (Fig. 5). MRI of the thoracic spine revealed a reduction in signal intensity on T2-weighted images with and without fat saturation within the paravertebral masses comparable to the thoracic spine after administration of superparamagnetic contrast media (Endorem; Guerbet, Sulzbach, Germany), indicating cells of the monocyte/macrophage system within the masses (not illustrated). A biopsy of the paravertebral masses was not performed due to thrombocytopenia. Enzyme replacement therapy with alglucerase (Ceredase; Genzyme, Cambridge, Mass.) was started in 1996 at a dose of 60 IU/kg body weight every 2 weeks. Two years later a clinical and radiological follow-up showed significant improvement in the general health status, laboratory values and skeletal involvement of the lower extremities. MRI of the thoracic spine showed a reduction of 5–8 mm in size of the paravertebral masses. On T2-weighted axial and coronal images, destruction of the vertebral cortex with a continuity between mass and vertebral body was detected (Figs. 6, 7).

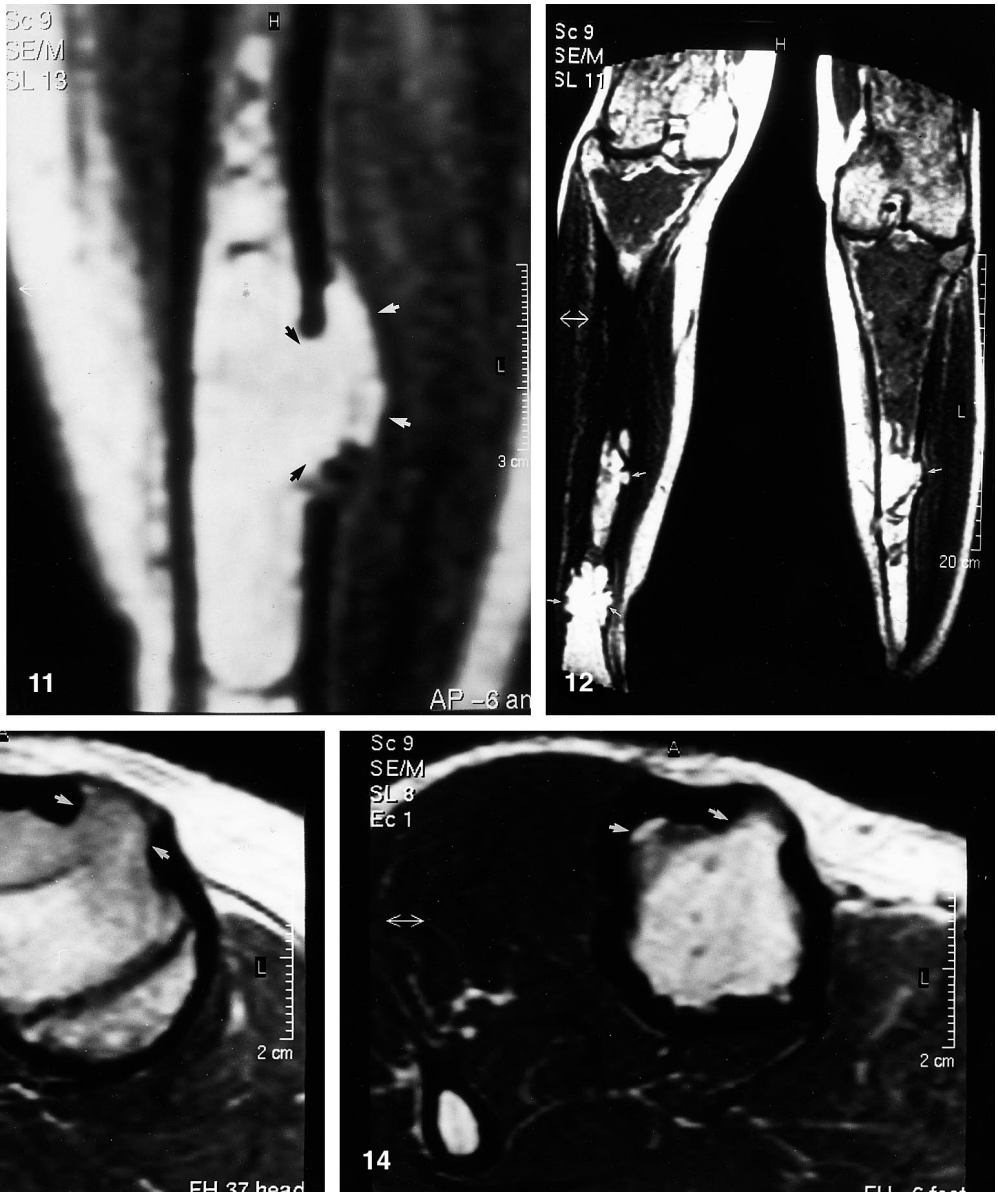


Fig. 11 Case 3. Magnification of Fig. 10 reveals a 2.2 cm neck of tissue (*black arrows*) with a cortical protrusion (*white arrows*)

Fig. 12 Case 3. T1-weighted image of the lower limbs in the coronal plane (slice thickness 5 mm) shows multiple extraosseous cortical extensions at the medial and lateral aspect of the right and left tibia (*white arrows*). Note the plaque-like abnormal low signal intensity in both tibial diametaphyses

Fig. 13 Case 4. Proton-weighted image in the axial plane (TR/TE: 1800/20 ms) of the left lower limb shows a focal cortical protrusion of the anteromedial aspect of the tibial cortex (*white arrows*)

Fig. 14 Case 4. Proton-weighted image in the axial plane (TR/TE: 1800/20 ms) of the left lower limb shows two focal cortical protrusions (*white arrows*)

Case 3

A 38-year-old man presented at our hospital for induction of enzyme replacement therapy. Gaucher disease type I was first diagnosed at the age of 4 years following splenectomy. The patient was complaining of severe bone pain, especially in both hips. Clinical examination revealed mild hepatomegaly and restricted movement of both legs. MRI of the hips showed extensive osteoarthrosis in both hip joints with severe deformity of both femoral heads and destruction of the greater trochanter with extraosseous extension into the left inguinal soft tissues (Fig. 8). MRI of the thighs revealed severe skeletal involvement with a consolidated pathological fracture of the right distal femur and a flask deformity of the left femur with a small lateral cortical protrusion (Fig. 9). The lateral aspect of the left tibial cortex (Figs. 10, 11) and the medial and lateral aspect of the right tibial cortex showed multiple localized cortical destruction with extension into soft tissue (Fig. 12).

Case 4

A 40-year-old woman was diagnosed as having Gaucher disease type I following splenectomy at the age of 19 years. Glucocerebrosidase activity in peripheral blood leukocytes was decreased on first admission. MRI of the lower extremities revealed an abnormal low signal intensity on T1- and T2-weighted images, indicating a de-

crease in fat marrow caused by Gaucher cell deposits. The anteromedial and anterolateral aspects of the right tibial cortex showed two focal protrusions of the marrow cavity into the cortical bone with cortical thinning and excrescence (Figs. 13, 14). The patient was complaining of severe diffuse bone pain and adynamia. Enzyme replacement therapy was started at a dose of 60 IU/kg body weight every 2 weeks. A follow-up after 16 months of enzyme replacement therapy showed an improvement in the adynamia, bone pain and skeletal disease. On follow-up, MRI did not reveal a change in the size of the two focal protrusions.

Discussion

The pathogenesis of bone changes in Gaucher disease is incompletely understood [9]. Histomorphometric studies reveal abnormal bone architecture with loss of trabecular connectivity, porous trabeculated cortices, increased cancellous eroded surfaces, and an increased number of osteoclasts [9]. A working hypothesis for the cause of bone disease relates to extensive intramedullary replacement of normal triglyceride with glucosylceramide-containing macrophages. Mechanical effects of the Gaucher cell infiltrates lead to an increase in intraosseous pressure [4] which, combined with local release of hydrolases and cytokines [9], contributes to the bone abnormalities. Generalized bone disorders including osteopenia, or frank osteoporosis, may result from systemic release of cytokines, particularly tumor necrosis factor and interleukin-6, which are known to be increased in some patients with Gaucher disease and which are potent stimulators of bone resorption [10]. Recent bone studies in adult patients with Gaucher disease type I revealed mean bone density values at the spine, hip, and forearm that were significantly lower than expected for age and sex [11]. However, serum concentrations of calcium, phospate, γ-carboxyglutamic acid-protein (bone-GLA protein), immunoreactive parathyroid hormone (IPTH), urinary calcium and hydroxyproline excretions have been shown to be normal [9]. These findings suggest that localized areas of increased bone resorption rather than a generalized derangement of bone turnover best explain the bone lesions in this disease.

In the present study, cortical and extraosseous extension with protrusion of the medullary cavity were seen eroding the inner margin of the cortex from inside to outside. A narrow neck of tissue, connecting marrow cavity and extraosseous extension, was apparent, indicating subsequent disruption of the cortex with soft tissue invasion.

Destruction of the lateral cortical mandible with extraosseous extension of Gaucher cells and plasma cell infiltrates into the right masseter muscle in our case 1 compares with a recent study in which 25 of 28 patients with Gaucher disease type I (89%) who underwent oral examination and orthopantomograms showed osseous lesions of the jaw. Common features in this study included enlarged marrow spaces, radiolucencies, endosteal scalloping and cortical thinning [12]. A possible explanation for the extraosseous extension in our case 1 is increased intramedullary pressure within the mandible and a release of hydrolases and cytokines leading to localized destruction of the corticle mandible. The fact that the recent medical history in this case had shown a submucosal abscess at this anatomical area raises the possibility that factors unrelated to skeletal Gaucher disease had evoked damage of the skeletal region.

Numerous case reports have documented the cooccurrence of Gaucher disease and lymphoproliferative disorders including chronic lymphocytic leukemia, multiple myeloma, lymphoma, Hodgkin disease and non-Hodgkin lymphoma [13–15]. Shiran and collaborators [16] demonstrated a 14.7-fold increased risk of hematological neoplasms and a 3.6-fold increased risk of other types of cancer in 48 patients with Gaucher disease as compared with 511 control subjects.

In case 2, multiple paravertebral masses were detected on CT and MRI and followed for 2 years, showing slight decreases in size. Areas of high signal intensity in the paravertebral soft tissue masses suggest a specific Gaucher mass rather than a malignant process. The uptake of iron oxides into the paravertebral masses indicates the existence of cells of the monocyte/macrophage system within the masses, suggesting benign osseous lesions – either extraosseous extension of Gaucher cells or extramedullary hematopoiesis. Although a biopsy was not performed, we preferred extraosseous Gaucher cell extension as primary diagnosis, because no obvious clinical and laboratory data suggested extramedullary hematopoiesis. Malignant entities such as lymphoma, leukemia, metastases or tumors of neurogenic origin were taken into the extended differential diagnosis, but seemed to be unlikely due to the uptake of superparamagnetic iron oxide within the masses. The slight decrease in mass size during enzyme replacement therapy corresponds to our own observation in a female Gaucher disease patient with a histologically proven epigastric “Gaucher cell pseudotumor” [8] that showed only a slight decrease in size after 2 years of enzyme replacement therapy (follow-up not yet published). According to the literature, only one case of intrathoracic extramedullary hematopoiesis has been described in an asymptomatic patient with Gaucher disease type I [17]. Hermann et al. [18] reported three adult Gaucher disease patients with epidural compression of the spinal cord. Comparable findings were published by Katz and coworkers [7], describing vertebral collapse with signs of root and cord compression in three children. In case 2, neither vertebral collapse nor an intraspinal mass was detected, as diagnosed by myelography, post-myelography CT and MRI.

In the present study, case 3 showed multiple cortical destruction with extraosseous extension at the lower extremities. Case 4 showed extension of the bone marrow cavity into the cortical bone with cortical thinning and excrescence but incomplete cortical disruption and no soft tissue extension. The morphological appearance in case 4 suggests an early stage of cortical erosion leading to cortical rupture and soft tissue extension.

Extraosseous extension with extravasation of Gaucher cells and formation of sinus tracts caused by cortical erosion mimicking malignancies was described by Hermann and coworkers [6]. In contrast to the patients reported by Hermann and coworkers, cortical and extraosseous extension rather than cortical erosion with soft tissue invasion were observed in this study. A unique case of juxtacortical osteoblastoma of the humeral shaft simulating extraosseous extension of Gaucher cell deposits has been reported by Kenan and coworkers [19]. Analysing MR images of the lower extremities in 70 Gaucher disease patients, we detected only two (3%; cases 3 and 4) showing extraosseous extension of the lower extremities, with an overall incidence of extraosseous extension in this series of 6%.

There is controversy about the role of splenectomy in the natural course of the bone infiltrate in Gaucher disease [4]. Theoretically, removal of the splenic storehouse of accumulating Gaucher cells should increase the load on the liver and bone marrow. In three of four cases we present, splenectomy was performed. Severe skeletal Gaucher disease was diagnosed in all four cases by MRI of the lower extremities.

It is important to emphasize that the site of emergence of the extraosseous tissue from bone was narrow in all four patients. This morphological feature may be helpful in distinguishing extraosseous Gaucher cell extension from other entities.

In conclusion, cortical protrusion and extraosseous extension of Gaucher cells is a rare manifestation of skeletal Gaucher disease. These rare skeletal manifestations, that may simulate malignant processes, should be considered in the differential diagnosis in Gaucher disease. The decision for biopsy should be based on clinical, laboratory and diagnostic imaging results.

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