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Gaucher Disease in Bone: From Pathophysiology to Practice

Introduction

- Today bone involvement in GD is known to be frequent: according to literature it occurs in approximately 75% of GD type 1 (GD1) patients.
- With the systematic use of various imaging modalities, the frequency of any bone involvement in GD1 has been reported to be more than 90% of patients.

- Bone involvement can also be seen to varying degrees in GD type 3 (GD3), whereas children with GD type 2 show no clinically relevant bone involvement because rapid neurological deterioration leads to death at 2–3 years of age, prior to the onset of bone pathology.

Pathophysiology of bone disease in GD

- Primarily, bone marrow is infiltrated by lipid-laden macrophages, called Gaucher cells.
- The spine, pelvis, and in particular the diaphyseal region of the femur and humerus are initially affected (Figs. 1 and 2).
- The progressive accumulation of glucocerebrosides within the bone marrow cavity leads to a progressive centrifugal expansion of the red bone marrow.

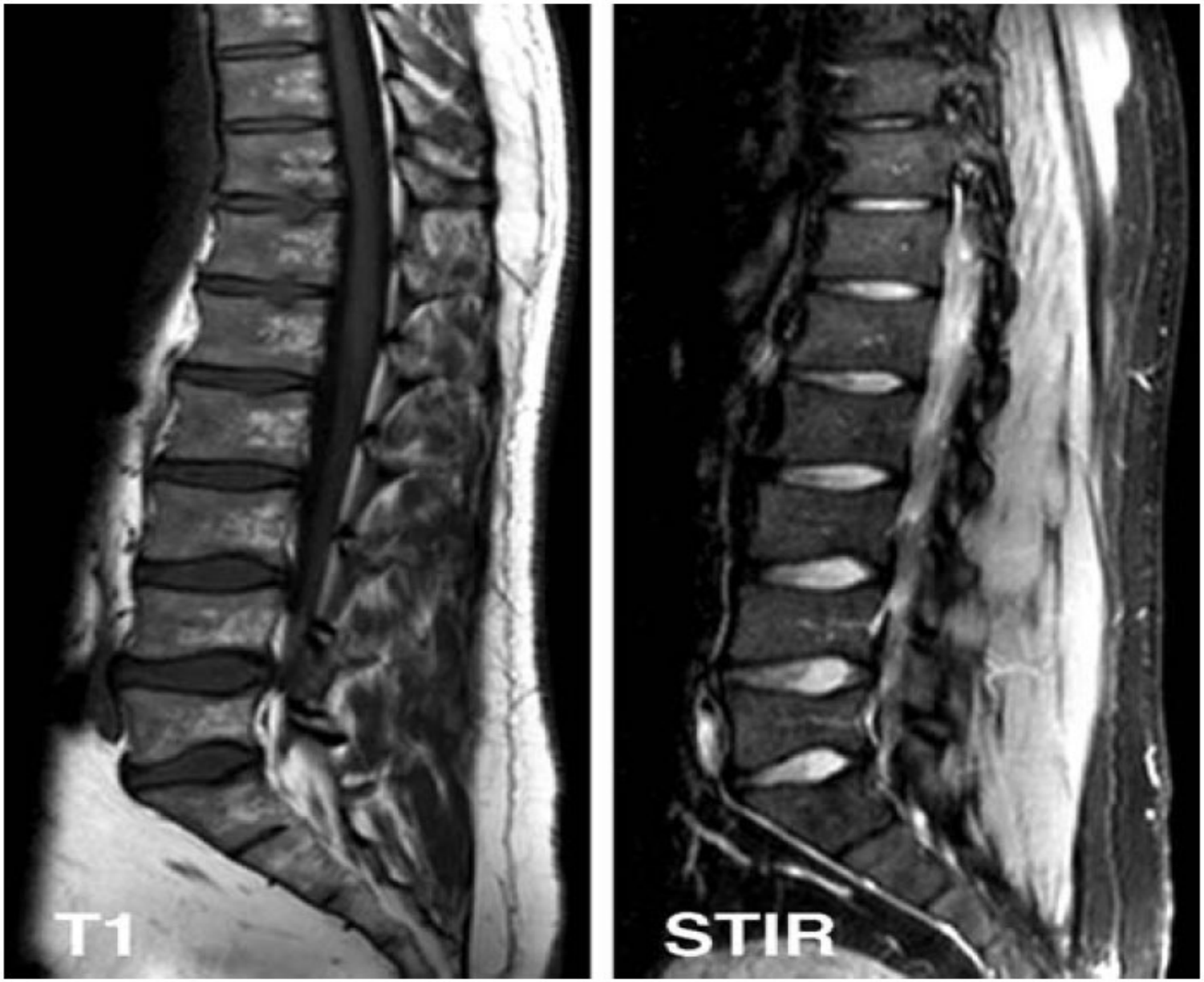


Fig. 1: MRI lumbar and thoracic spine, T1 and STIR images: Bone marrow infiltration by Gaucher cells showing diffuse hypointensive signals in the T1 and STIR images with sparing around the area of the basivertebral vein in the T1 images. BMB score 4

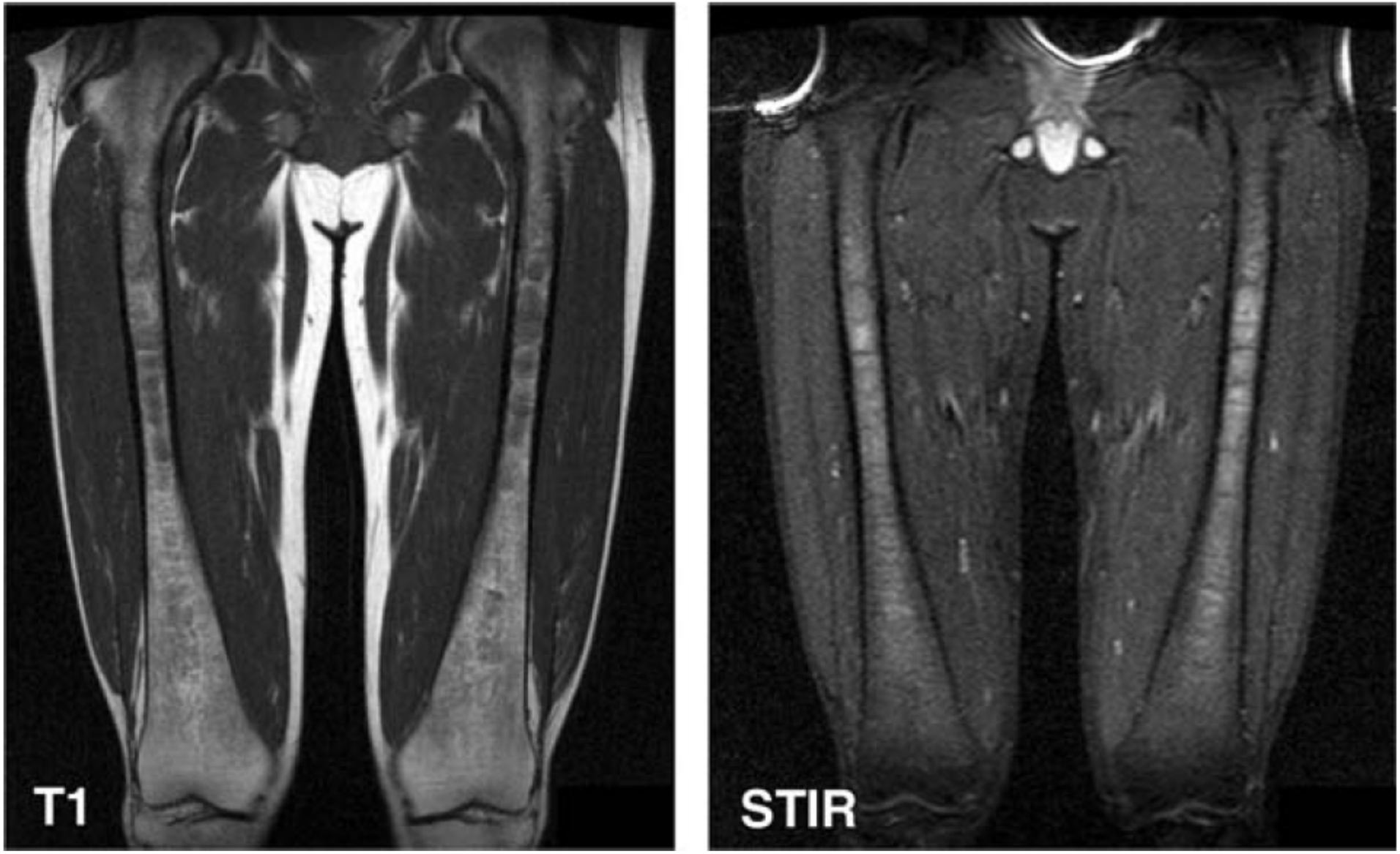


Fig.2: MRI femora, T1, and STIR images: extensive diffuse low-to-intermediate low T1 signals and increased STIR signals within the diaphyses of both femora. Note the sparing of both epiphyses. BMB score 5

- The displacement of inactive yellow marrow by red marrow in the periphery alters vascularity and local pressures possibly leading to localized thrombosis or infarction by Gaucher cells.
- Pathologies such as bone crises, avascular necrosis, bone infarcts, and localized cortical thinning may be explained in part by these effects.

- In addition, glucocerebrosidase accumulation seems to induce macrophage activation, which may promote additional inflammatory processes due to the altered expression of different macrophage-derived factors and cytokines.
- The activity of osteoclasts and osteoblasts are influenced by a variety of hormones including estrogen, testosterone, parathyroid hormone, or thyroid hormone.

- The effects of hormones on the skeleton can be mediated either directly by hormone receptors located on osteoblasts and osteoclasts or indirectly by various other cells of the immune system.
- Changes of cytokines including inflammatory mediators, such as interleukin (IL)-1, IL-6, and tumour necrosis factor-alpha (TNF-a), consequently influence osteoclast and osteoblast activity.

- Overall, this cross-talk of immune cell–osteoclast/ osteoblast interactions, known as osteoimmunology, reveals bone metabolism to be a complex network of interacting factors including bone marrow and immune and bone cells.
- In GD, the complex interactions of cells of the bone marrow with bone as two separate compartments closely interacting with each other may explain some of the changes seen in bone disease with GD.

Gaucher disease and bone manifestation

- The skeletal manifestations of GD include a variety of bone pathologies due to the progressive glucocerebroside storage, changes of vascularity, and impaired bone remodeling as described above.
- Bone manifestations in GD include bone infarcts, avascular bone necrosis, cortical thinning, lytic bone lesions, osteosclerosis, fractures due to osteopenia orosteoporosis, and rarely acute osteomyelitis.

- Furthermore, growth retardation during childhood and extraosseous manifestations of bone disease should be mentioned.
- In most patients bone disease in GD shows a progressive course over years.
- Overall, the bone manifestations in GD are one of the most debilitating aspects of the disease.

- From a clinical point of view GD patients frequently face acute or chronic episodes of dull, achy bone pain of varying intensity.
- The clinical symptoms of bone disease in GD and its complications such as bone crisis, avascular necrosis with joint destructions, or fractures place a heavy burden on the patients quality of life.

- In a review on the skeletal aspects of GD Wenstrup et al divided the bone pathologies associated with GD into three groups:
- >>(a) focal disease (irreversible lesions, e.g., osteonecrosis, osteosclerosis),
- >>(b) local disease (reversible abnormalities adjacent to heavily involved marrow, e.g., cortical thinning, bone deformities),
- >> (c) generalized osteopenia.
- However, this descriptive and morphologically orientated division of bone pathologies in GD does not explain the different pathologies.

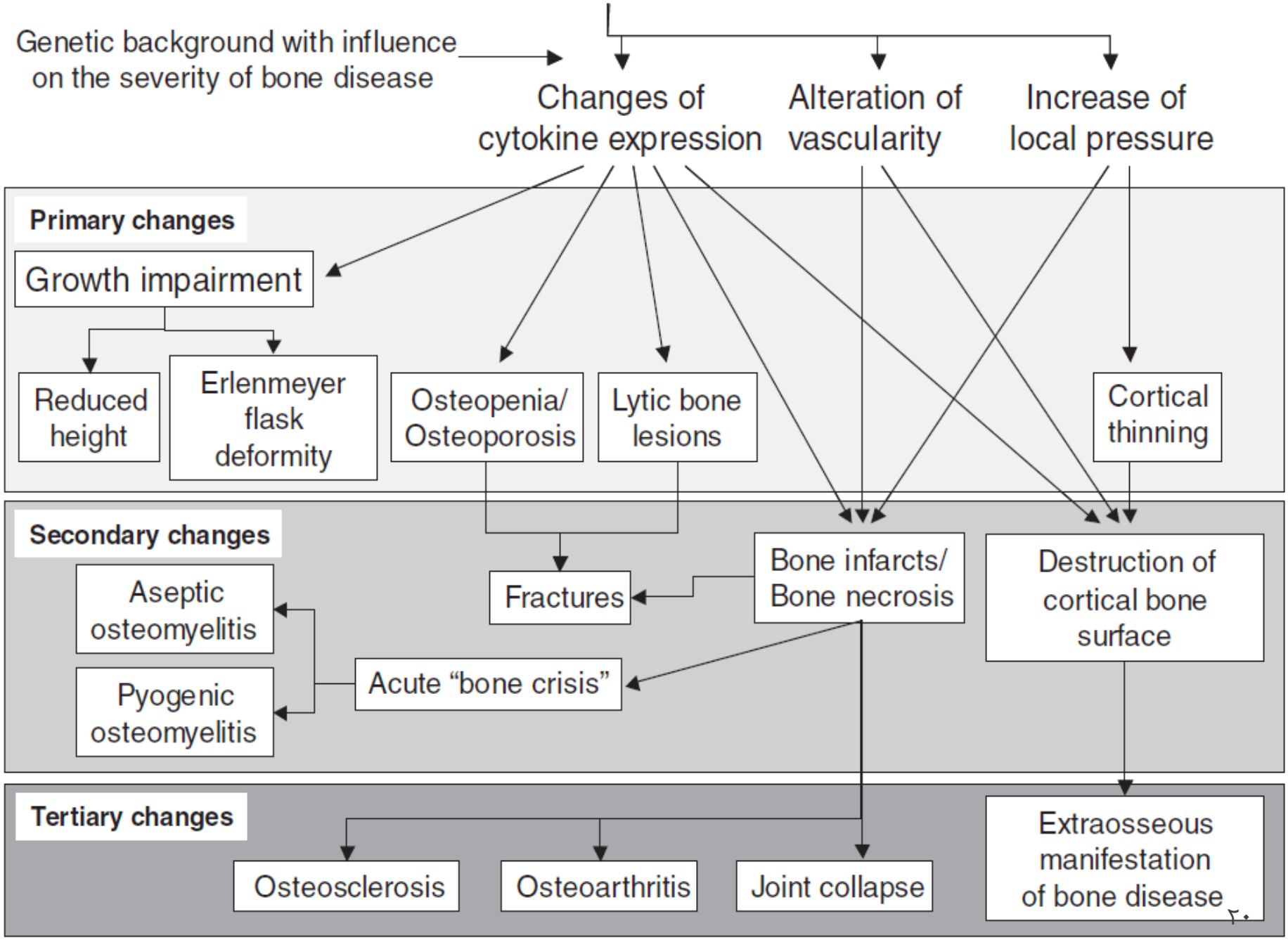
- Alongside this division, based on current knowledge the development of bone pathologies in GD might also be seen as a sequence of events (Fig. 3).
- Bone pathologies seen in GD may be divided into primary, secondary, and tertiary changes.

- Primary changes are likely to be due to altered cytokine expression or increased local pressure.
- Upon enzyme replacement therapy (ERT) these pathologies are at least partly reversible.

- Secondary changes, such as bone infarcts, may evolve out of complex pathological mechanisms including changes of cytokine release, alteration of vascularity, and increased local pressure due to extensive glucocerebroside accumulation.
- Clinically, these pathologies are acute events often accompanied by severe bone pain.

- Tertiary changes summarize those rather chronic pathologies seen as further deterioration evolving out of secondary, firstly acute, changes.
- Secondary and tertiary changes will leave scars within the bone and bone marrow, which will remain unchanged even on ERT.

Accumulation of Gaucher cells in bone marrow cavity



Growth retardation during childhood

- Growth retardation has been reported in GD.
- After initiation of ERT most patients showed growth acceleration and regained normal weight.

Erlenmeyer flask deformity

- The Erlenmeyer flask deformity (EFD) describes a distinct abnormality of the distal femora (Fig. 4).
- It can also be seen on occasions within the metaphyseal region of other tubular bones, in particular the proximal tibia.
- EFD results from impaired modeling within the di-metaphysis and abnormal cortical thinning, due to local bone marrow infiltration by Gaucher cells.
- This leads to a lack of the typical concave di-metaphyseal curve resulting in an Erlenmeyer flask-like appearance.
- EFD, although common in GD, is not pathognomonic for GD.
- Recently Faden et al, described 20 distinct disorders associated with EFD.

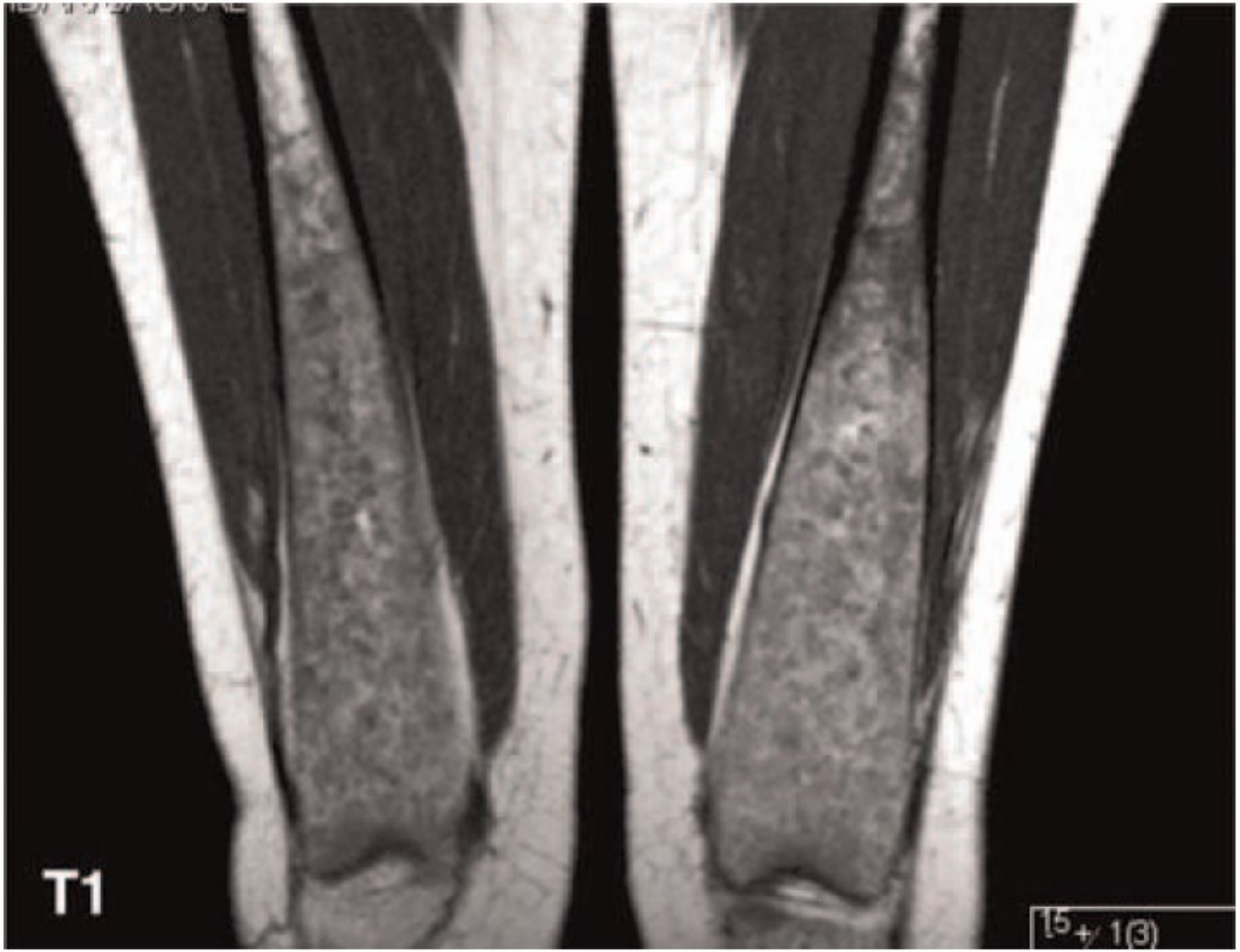
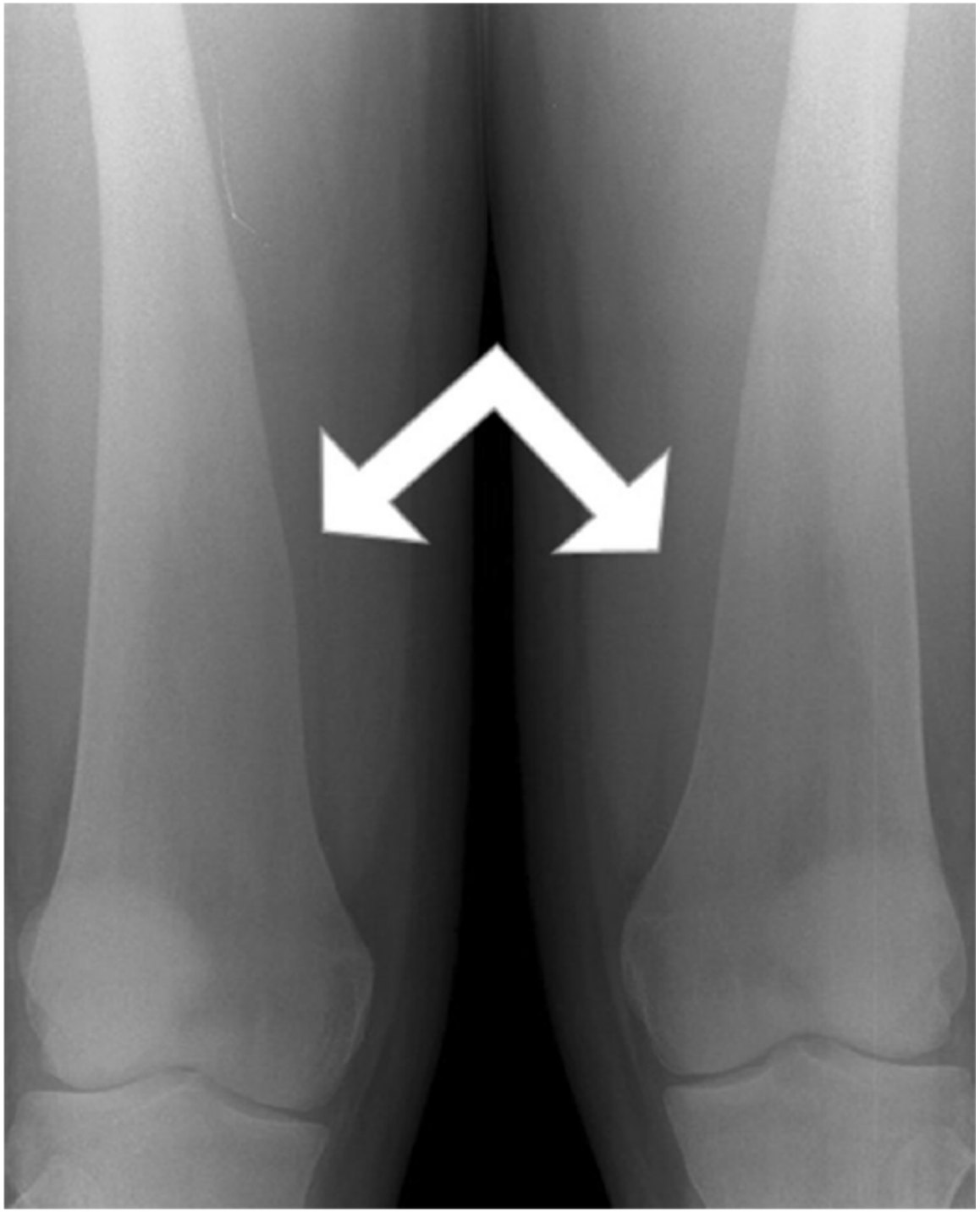


Fig. 4: MRI femora, T1 image: Erlenmeyer flask deformities in both femora with loss of tabulation; additionally, patchy infiltration of both femora due to extensive Gaucher cell infiltration



Osteopenia, osteoporosis

- Reduced bone density is common in GD and is associated with an increased risk of fracture (Fig. 5).
- Generalized osteopenia correlates with overall disease severity;
- Vertebral density was an independent predictor of the severity of bone involvement.

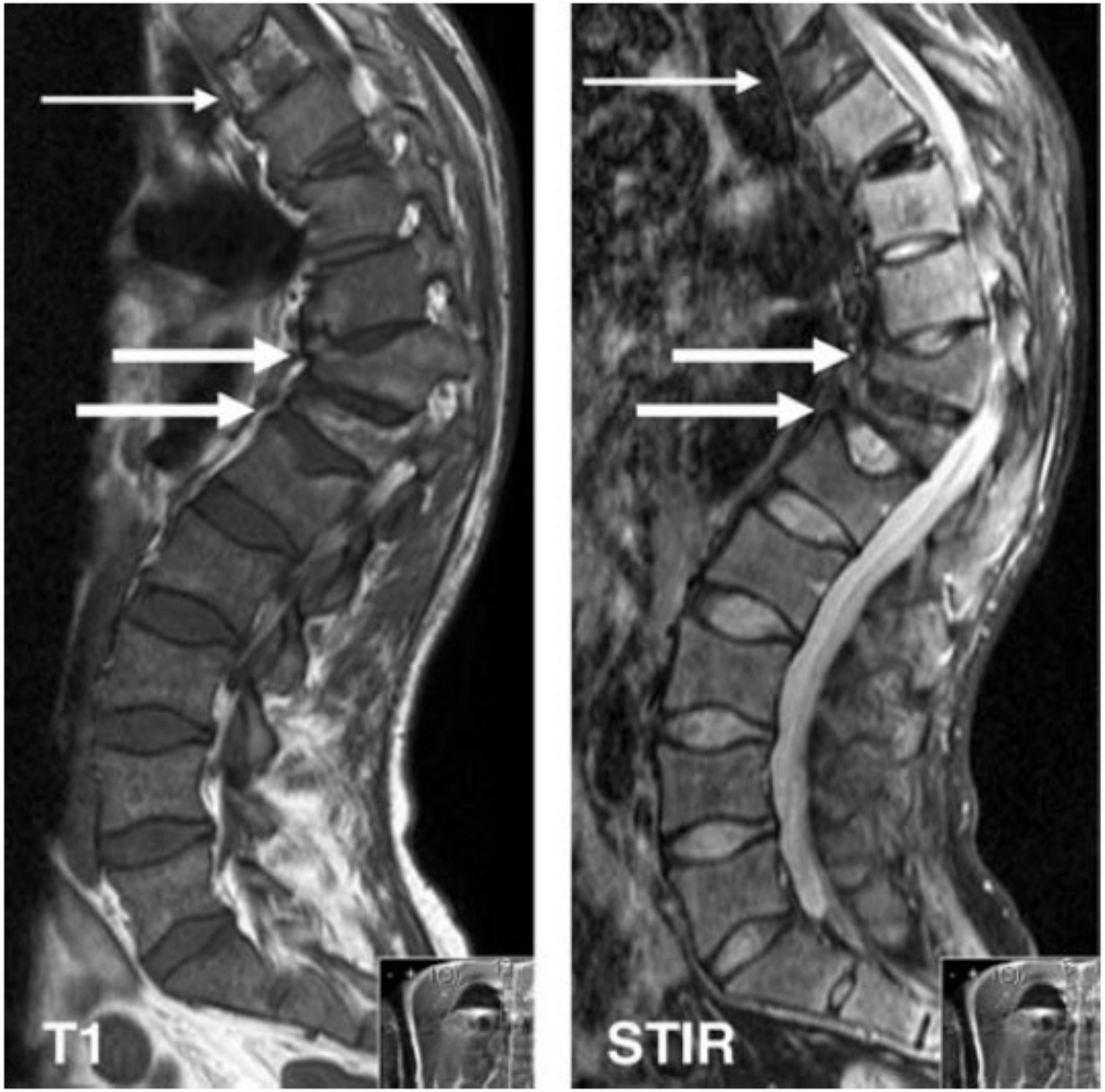


Fig. 5: MRI lumbar and thoracic spine, T1 and STIR images: Hypointense signals in the T1 and STIR images throughout the spine indicative of diffuse bone marrow infiltration by Gaucher cells. Collapsed vertebra Th11 and Th12 resulting in a marked kyphosis; L1 also reveals a fracture of the upper end plate (large arrows). Signal alterations in Th7 associated with an old bone infarct (small arrow). BMB score 6

Osteolytic lesions

- Focal osteolytic lesions are frequently seen in GD, which may be combined with other localized pathologies such as cortical thinning or bone extensions (Fig. 6).
- Increased cathepsin K excretion by activated osteoclasts may play a role in the development of osteolytic lesions.

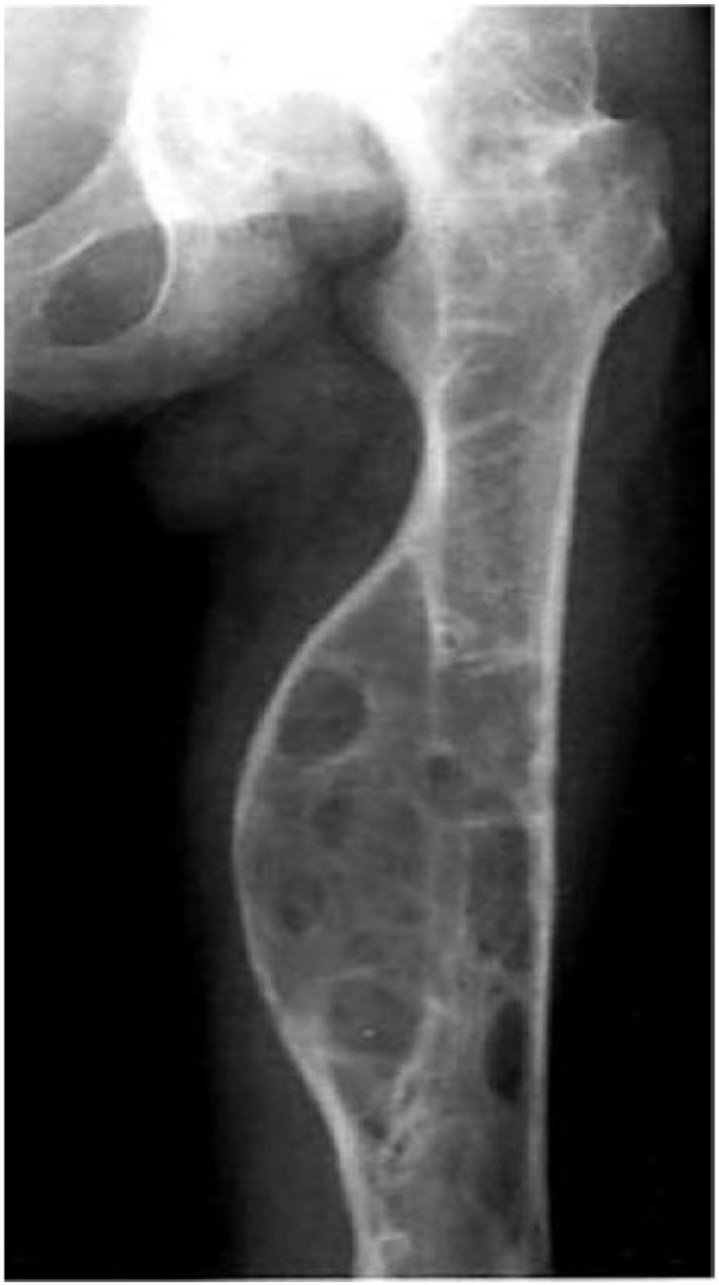


Fig. 6: X-ray of femur: Within an osseous extension cortical thinning and several lytic lesions are present giving a honey woven pattern. Such lesions are due to extensive accumulation of Gaucher cells

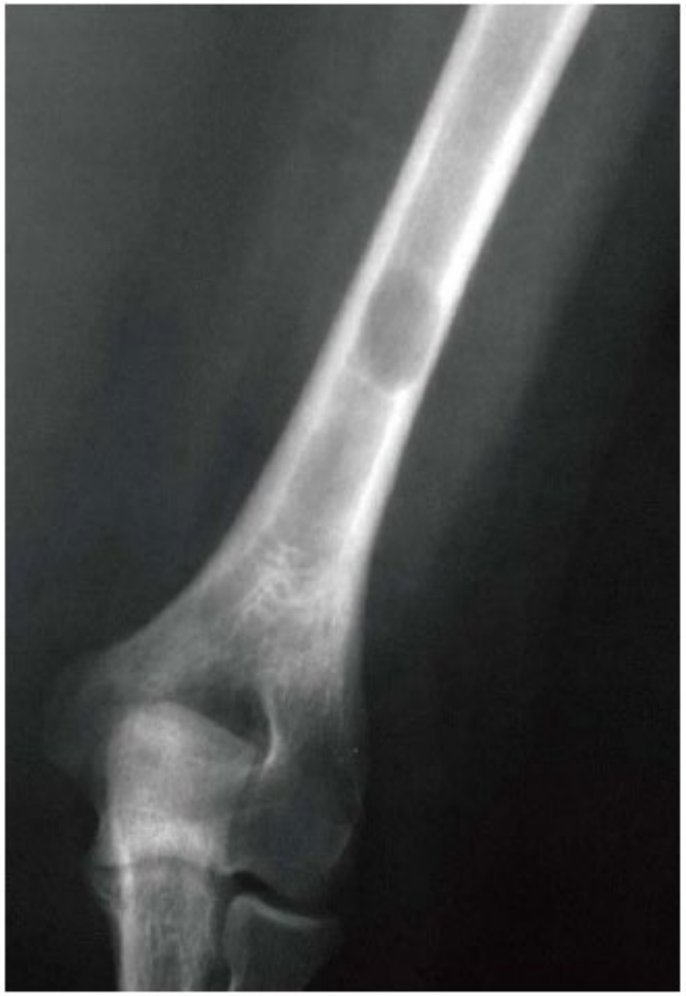


Figure 5 Lytic lesion. Frontal radiograph of the distal right humerus demonstrates a well demarcated lytic lesion that does not show sclerotic borders, endosteal erosion or associated expansion of the humeral shaft.

Bone infarcts, osteonecrosis, osteosclerosis, osteomyelitis

- Infarction by Gaucher cells, alterations of vascularity including thrombosis, and possible additional inflammatory processes lead to bone infarcts (Fig. 7).
- These may occur without any clinical symptoms or only slight pain.

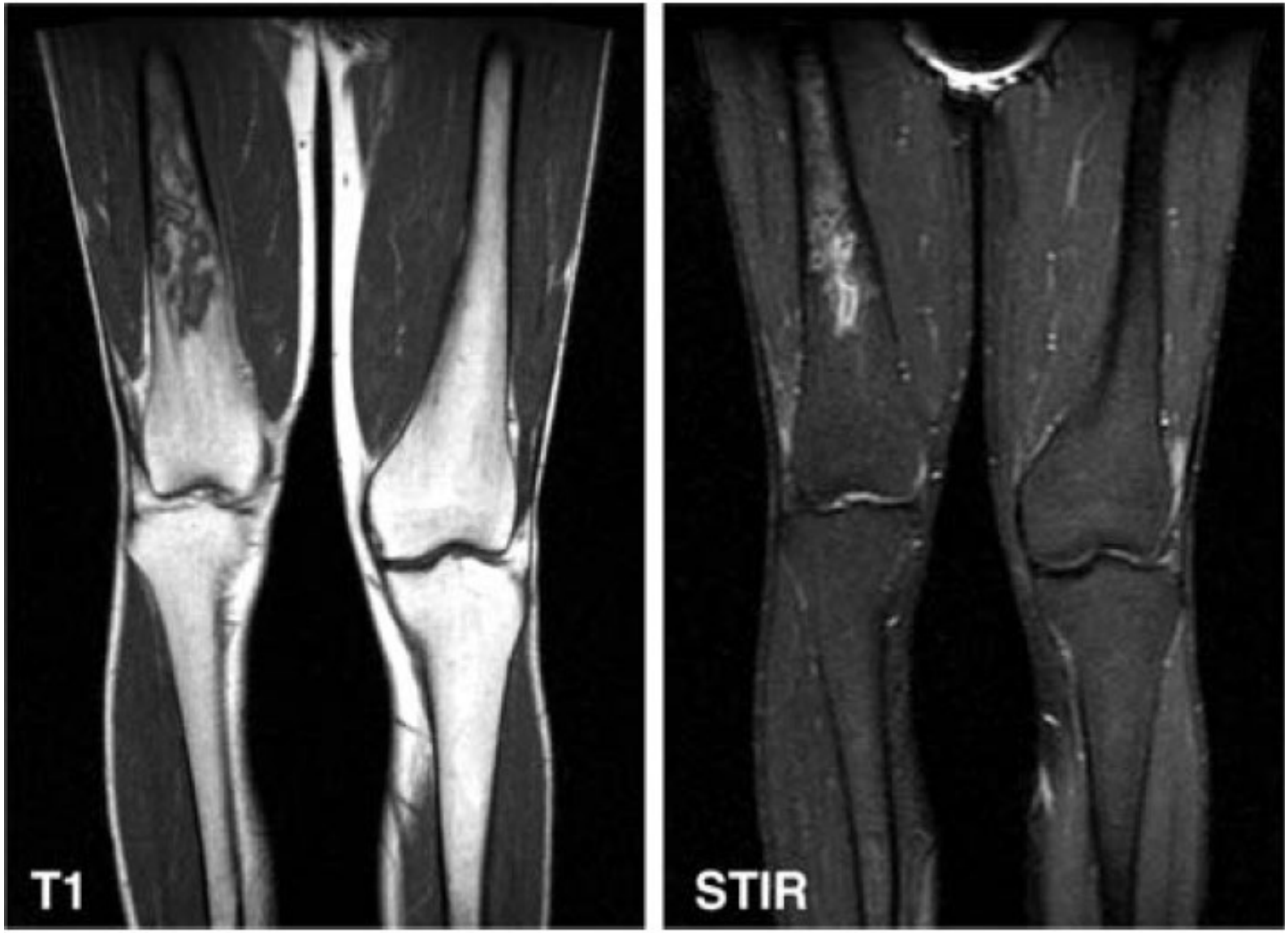


Fig. 7: MRI femora, T1, and STIR images: normal appearance of the left femora, whereas in the right femora within the diaphyseal region a bone infarct is seen; also slightly increased STIR signal associated with Gaucher cell infiltration. BMB score 4

- However, in GD patients bone infracts may also present with sudden onset of localized pain, tenderness, erythema, and swelling.
- Such acute episodes of severe bone pain are frequently accompanied by fever, elevated leukocytes, and an accelerated erythrocyte sedimentation rate.
- This acute focal bone involvement of GD, also called bone crisis, can result in aseptic osteomyelitis.

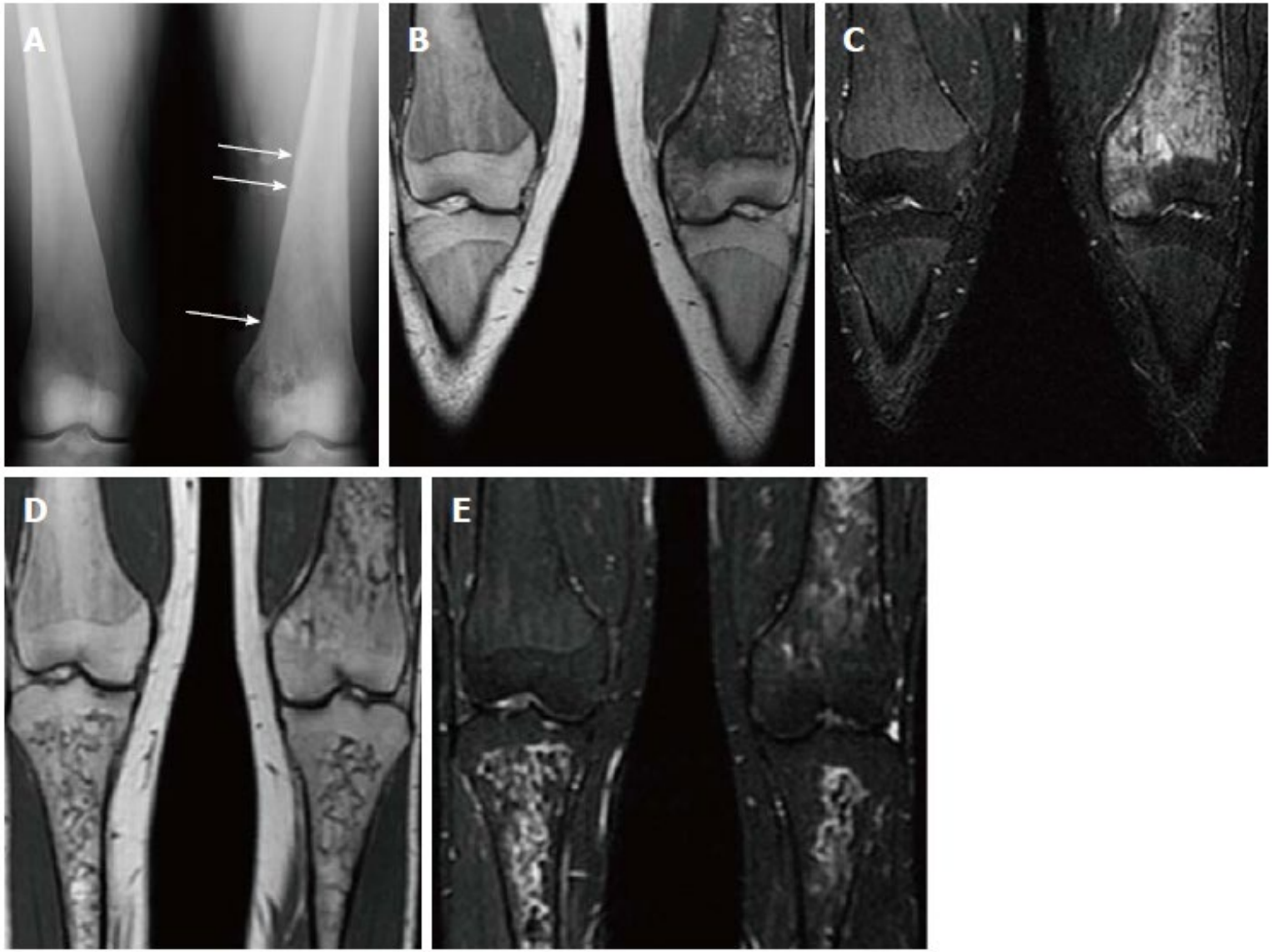


Figure 10 Psuedo-osteomyelitis. Frontal radiograph of both distal femurs in 2009 (A) demonstrates an irregular area of patchy lucency in the medial condyle of the left femur. There is periosteal reaction in this area as well as more superiorly (arrows). Coronal T1 WI (B) image at the same time in 2009 demonstrate low SI in the medial condyle of the femur extending into the medial epiphysis. There is high SI in these areas on coronal STIR (C) image which extends into the adjacent soft tissues where the periosteal reaction is seen on the radiograph. There is no joint effusion. The patient presented with left knee pain and the imaging was suspicious for osteomyelitis involving the medial distal femur. However, the patient has no fever and cultures were negative. Coronal T1 WI (D) of the same area in 2011 shows resolution of the low SI in the medial condyle and epiphysis. The corresponding high SI on the STIR image (E) has resolved as well.

- Osteonecrosis is believed to be secondary to ischemia due to chronic infarction.
- It is an irreversible process and predominantly affects the femoral head, proximal humerus, and vertebral bodies, resulting in possible fractures and joint collapse (Fig. 8).

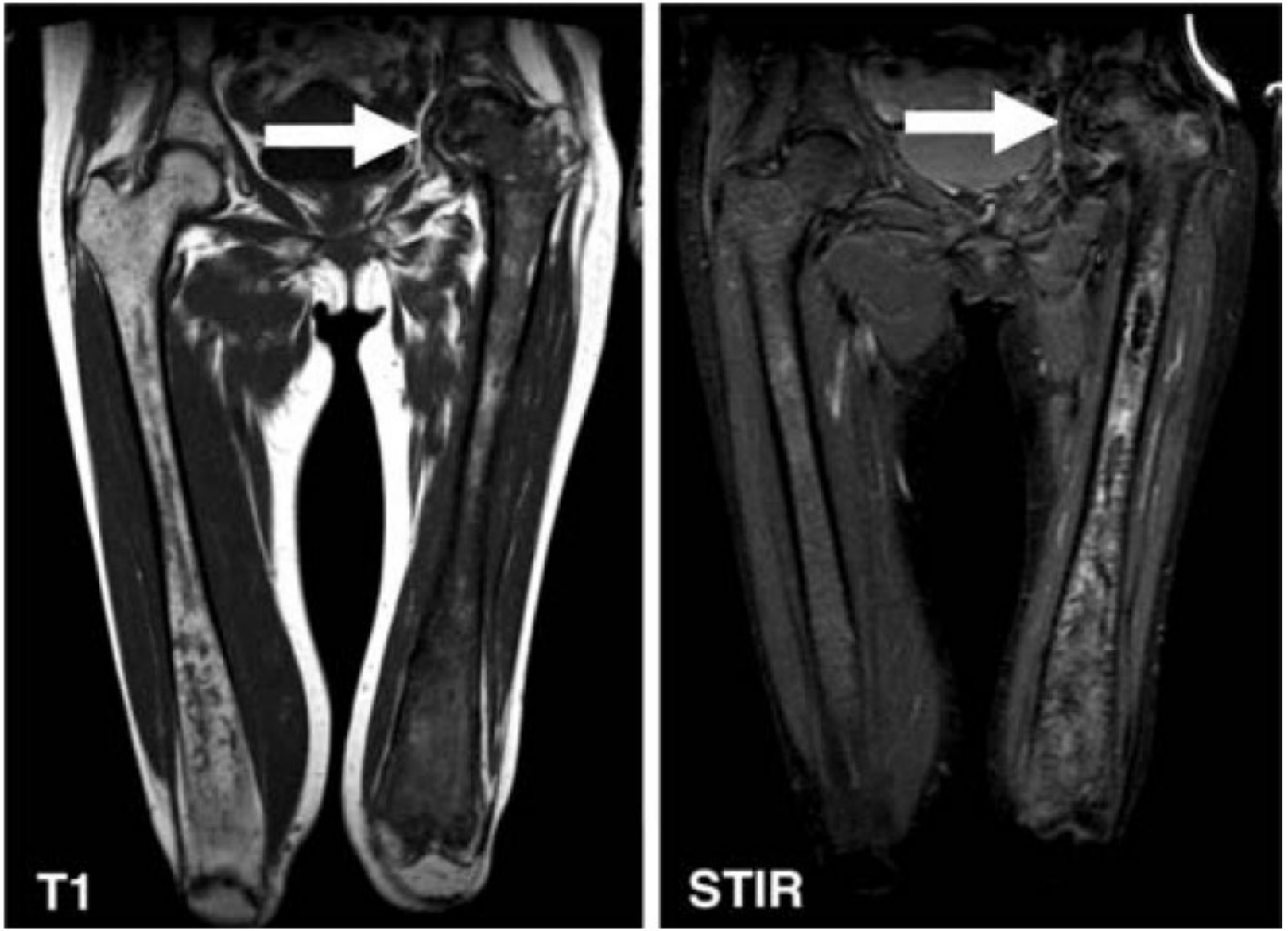
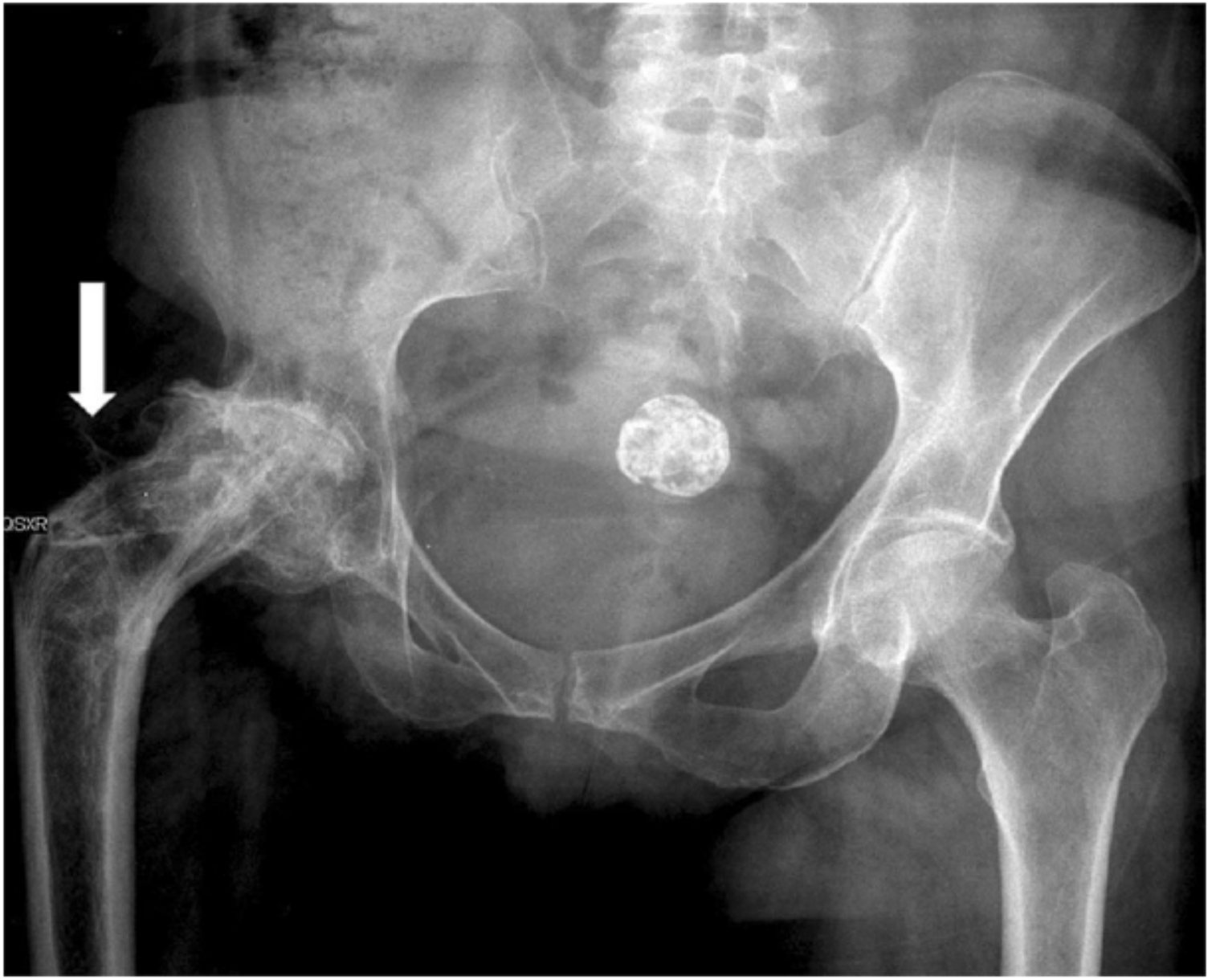


Fig. 8: MRI femora, T1, and STIR images: Hypointense signals due to extensive bone infarcts in the left femora and, to some extent, also in the right femora in the T1 images. The left hip reveals avascular necrosis with joint deformation (arrow). BMB score 3 (excluding the bone infarcts)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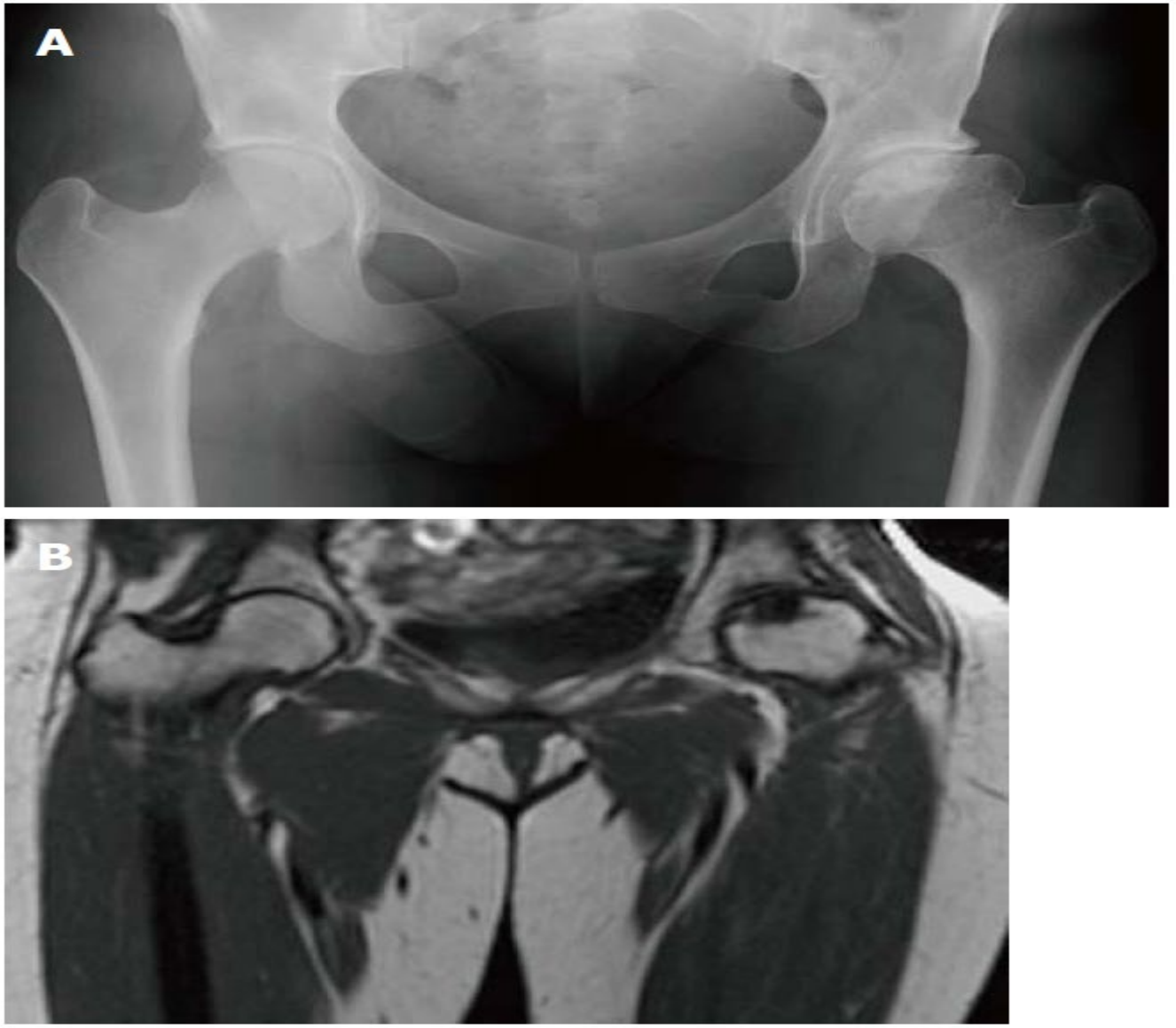

Figure 6 Osteonecrosis. Frontal radiograph of the pelvis (A) shows avascular necrosis of the left femoral head. The femoral head has a flattened contour with sclerosis in the subcapsular areas. Note that the joint space is maintained. Coronal T1 WI (B) in the same patient again demonstrated an abnormal shape of the left femoral head with flattening superiorly. In the same area there is a focus of low SI indicating the devascularized bone.

- Additionally, after bone infarction focal osteosclerosis or osteoarthritis may occur depending on the location of the bone infarct.

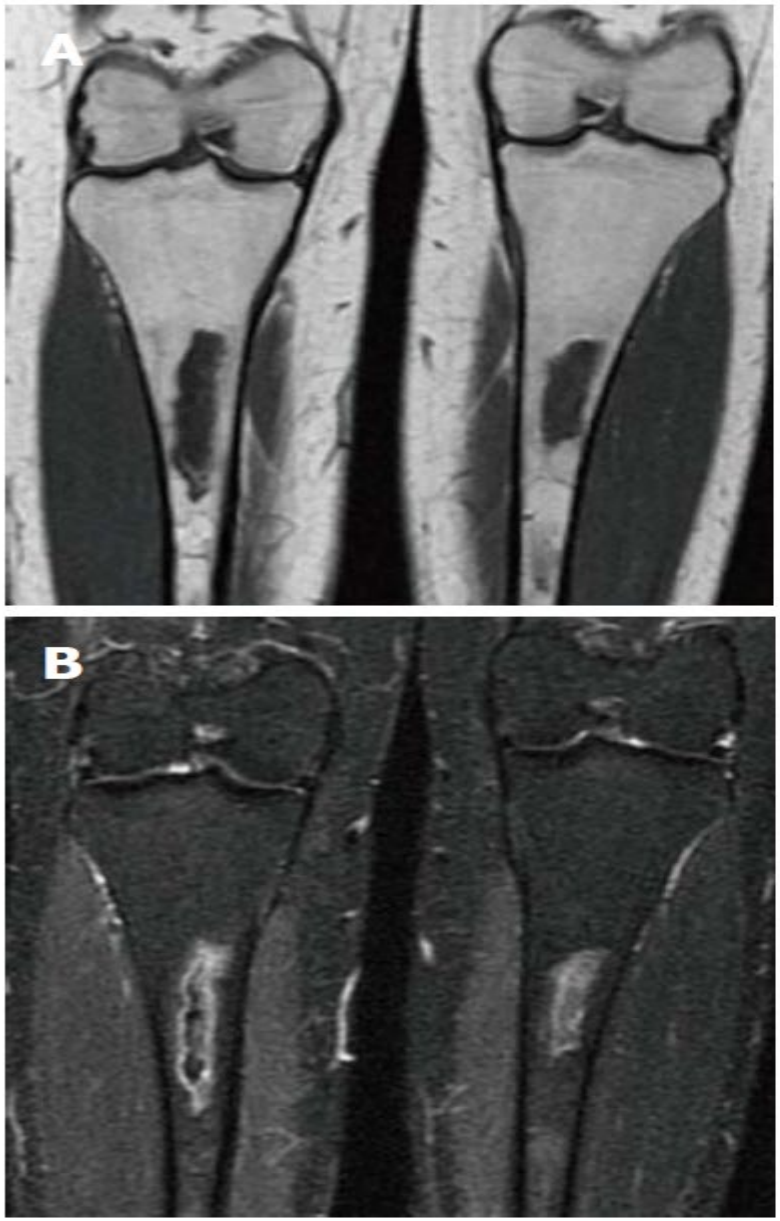

Figure 7 Medullary infarction. Coronal T1 WI (A) image shows irregularly bordered areas of low SI within the medullary cavity of both tibiae. The same areas show peripheral serpigenous high SI on the coronal short tau inversion recovery (STIR) (B) image. The appearance is typical of an infarct.

Cortical thinning and long bone deformity

- Cortical thinning and long bone deformity can be frequently seen in areas adjacent to bone marrow infiltration.
- Increased local bone marrow pressure due to extensive glucocerebrosidase accumulation and possibly also locally activated osteoclasts may play a role in the development of this bone pathology.

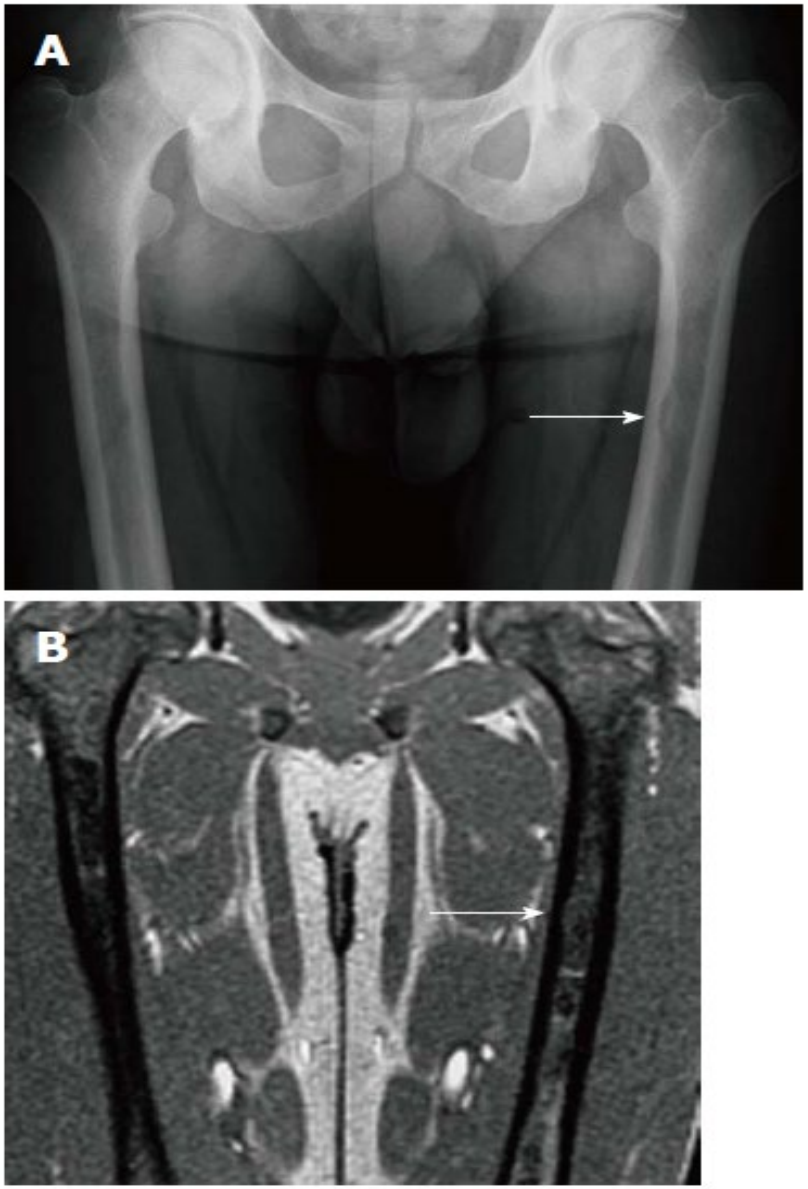

Figure 8 Endosteal scalloping. Frontal radiograph (A) of the femurs shows an area of rounded thinning of the medial cortex of the left femur (arrow). Coronal out of phase image of the femurs in the same patient (B) shows low signal intensity in that same area due to expansion of the medullary cavity due to infiltration. The thinning of the cortex is less apparent on magnetic resonance than on radiography.

Extraosseous manifestation

- A very rare skeletal manifestation in GD is an extraosseous extension of Gaucher cells, which occurs after cortical destruction and extraosseous extension into tissue adjacent to the bone (Fig. 9).

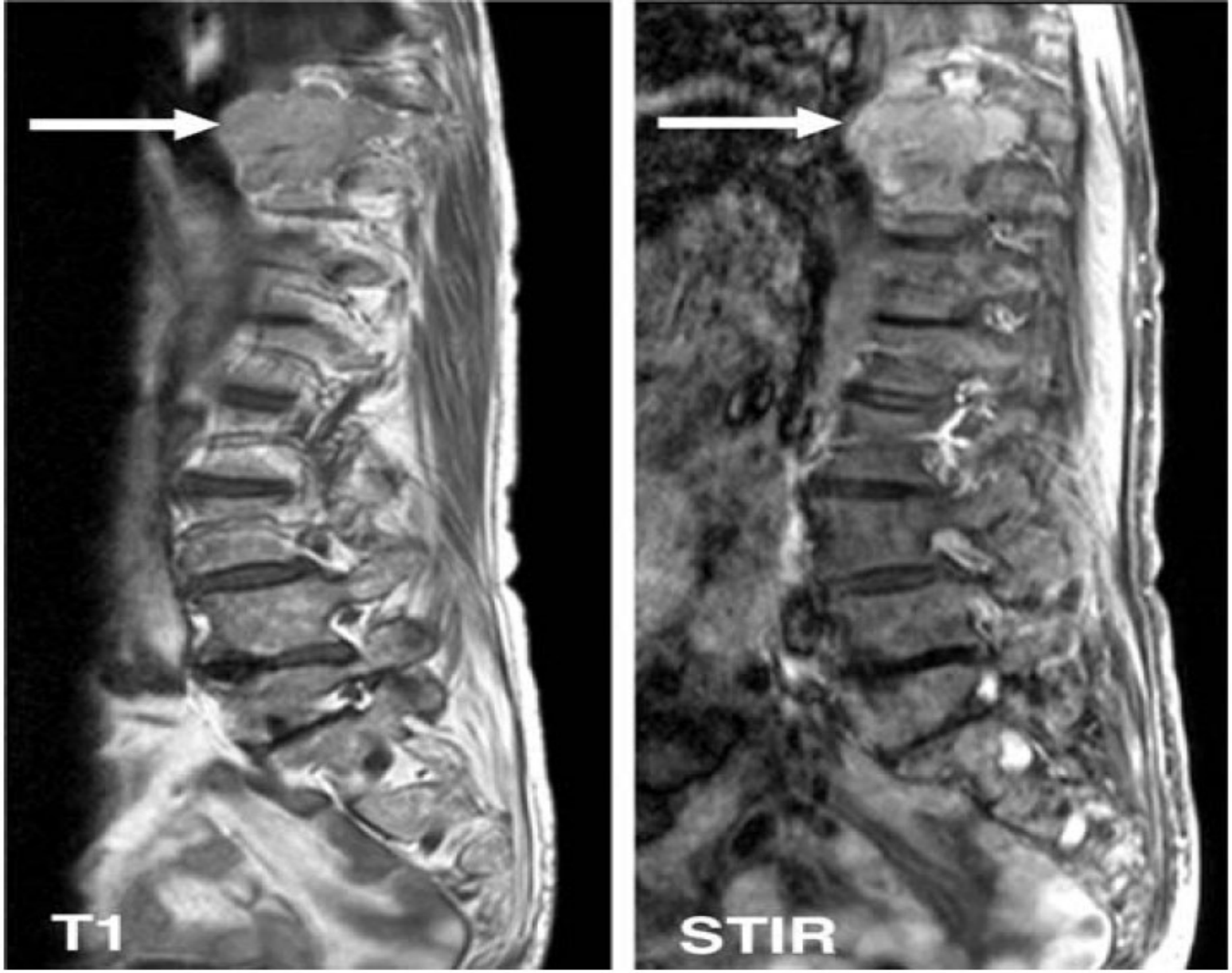

Fig. 9: MRI lumbar and thoracic spine, T1, and STIR images: Patchy low T1 and STIR signals in the entire spine due to Gaucher cell infiltration. In addition, extraosseous extension presenting as a tumorous mass measuring about 5 cm in diameter adjacent to Th10/T11 (arrow). The lesion shows extramedullary hematopoiesis and remains constant over years

- Likely cortical thinning promoted by increased local pressure, altered vascularity, and increased cortical porosity due to cytokines activating osteoclasts may precede cortical destruction.
- It has to be regarded as a manifestation of severe bone disease, and so far, only few cases have been described.

- The differential diagnoses for extraosseous extension include osteomyelitis and hematological malignancy.
- MRI and the biopsy of the lesion, or, if clinically necessary, its surgical removal, will lead to the diagnosis.

Diagnostic approaches to bone manifestations in GD

- The extent of bone involvement in GD cannot be estimated solely by clinical examination, thus necessitating bone imaging.
- Imaging of bone and bone marrow in GD aims to evaluate the disease burden, to show up the presence of skeletal complications and to follow up treatment effects on bone disease.
- A number of imaging modalities are available for the evaluation of bone manifestation in GD.

X-ray

- Plain radiography is broadly available and inexpensive, but it shows a low sensitivity in detecting skeletal pathologies in GD.
- However, it can be used in the detection of bone complications such as fractures or dislocation of joint replacements.
- It is regarded as the method of choice for the evaluation of joint arthroplasty .
- Furthermore, X-ray can detect local deformities of bone including Erlenmeyer flask deformity, cystic or tumorous lesions, and localized cortical thinning.

Magnetic resonance imaging (MRI)

- MRI can visualize with high sensitivity all kinds of morphological bone manifestations seen in GD.
- Different MRI modalities are used in the evaluation of bone involvement in GD.

- The infiltration of bone marrow by Gaucher cells creates hypointense signals.
- Patients on ERT show a normalization of signal intensity due to the reduction of Gaucher cell deposition and increase in fatty yellow marrow.
- MRI is the method of choice to evaluate the extent of bone disease prior to therapy and during follow-up in patients on therapy.
- It is also the most sensitive method to detect femoral head necrosis.

Scintigraphy

- Although scintigraphic methods are not recommended as first-line methods for the evaluation and follow-up of bone disease in GD , they can be used for specific clinical questions.
- As an alternative to MRI, 99 mTc-methylene diphosphonate (99 mTc-MDP) bone scintigraphy can be used in the discrimination of osteomyelitis and avascular necrosis if performed 72 hours after clinical onset , adding significant information in this setting, since discrimination of these two conditions by clinical means is often difficult or impossible.

- Further applications of bone scintigraphy include the detection of occult fractures or the evaluation of loosening of hip joint prostheses, in which case 3-phase bone scintigraphy should be applied.

- Bone marrow scintigraphy indirectly visualizes the bone marrow infiltration by Gaucher cells by imaging the extent of bone marrow displacement.
- The lipophilic tracer 99 mTc-methoxyisobutyl (99 mTc-MIBI) directly images the glycolipid deposits due to Gaucher cells, thus being useful for the quantification of bone marrow infiltration prior to therapy and during follow-up on ERT.

- Direct imaging of bone marrow infiltration by Gaucher cell deposits by 99mTc-MIBI scintigraphy is also of particular interest in children in whom bone marrow undergoes a developmental conversion from red to yellow marrow in the appendicular skeleton.

- Thus, MRI interpretation is more difficult in young GD patients than in adults in estimating the exact amount and extent of bone marrow infiltration by Gaucher cell.
- Furthermore, scintigraphy could be used as an alternative to MRI in those patients who cannot undergo MRI imaging (e.g., pacemaker, joint replacements, or claustrophobia) and in places with limited access to MRI.

Osteodensitometry (DXA)

- Bone mineral density (BMD) measured by osteodensitometry (DXA) has a central role in the quantification of bone loss and the diagnosis of osteoporosis.
- The extent of osteopenia correlates with clinical indicators of disease severity including prior splenectomy .
- Further studies have confirmed these findings in GD patients showing decreased BMD at different sites (lumbar spine, neck, trochanter, distal radius).
- So far, there are no studies available that correlated reduced BMD with fracture risks in GD patients.

Bone biopsies

- For the routine diagnostic work-up of bone disease in GD bone biopsies are only of relevance where lesions suspicious for malignancy and unamenable to other imaging are under investigation.

Other diagnostic modalities relevant for evaluating bone disease

- Quality of life could be assessed using SF-36 survey.
- Furthermore, as pain is a frequent clinical symptom associated with bone disease in GD, assessment of pain using scaling systems such as the visual analog scale (VAS) or narrative analog scale (NAS) should also be used in routine follow-ups of GD patients.
- This would ensure adequate pain management, comparison of pain level between follow-ups, and better quantification of treatment effects.

Which methods should be applied at which time?

- MRI scanning is the method of choice for baseline evaluation and follow-up.
- MRI scanning of the spine, the femora, and eventually also the pelvis, is generally recommended at baseline.
- Patients should be followed up every 24 months, if possible even every 12 months;
- furthermore, those patients receiving ERT should be assessed at times of dose adjustments.
- The Düsseldorf Score is useful in the evaluation of the extent of bone marrow involvement within the lower extremities.

- Scintigraphic methods, although not generally used for investigations in GD, can be performed for specific questions as outlined above, in particular if MRI cannot be performed or is not available.

- Plain radiographs can be used to detect bone complications such as fractures or bone deformities, but due to its low sensitivity in detecting bone disease in GD, the routine use of X-ray is not recommended in the diagnosis and follow-up of GD neither in children nor in adults.
- However, when MRI scanning is not available (e.g., in developing countries), X-rays may be the only available alternative to follow up bone disease in GD.

- DXA scanning is generally recommended for the evaluation and follow-up of GD patients.
- According to the recommendations given, scans at 1- to 2-year intervals are advised.
- However, as BMD changes can be expected to evolve only after several years, longer intervals should be considered based on the least significant change (LSC) of DXA measurements.

- As other pathological conditions are frequently present in GD at the sites of DXA measurements (lumbar spine, hip), complimentary evaluation of these regions by either X-ray or MRI in order to exclude pathologies, which cause false high BMD results (e.g., vertebral fractures, avascular necrosis of the hip), needs to be performed for adequate DXA interpretation.

Therapeutic effects on bone in GD

Treatment goals

- Therapeutic goals concerning the bone manifestations in GD1 include:
- (a) the reduction or elimination of bone pain within 1–2 years,
- (b) the prevention of bone crises,
- (c) the prevention of osteonecrosis and subchrondral joint collapses,
- (d) the improvement of BMD (pediatric patients: attain normal or ideal peak skeletal mass, and increase cortical and trabecular BMD by year 2; adult patients: increase trabecular BMD by 3–5 years).

- The effects of any therapy should also be interpreted according to the underlying changes.
- Based on the differentiation of bone changes in GD into primary, secondary, and tertiary changes, as outlined above, ERT should aim to resolve in particular primary changes and to prevent secondary changes.
- However, secondary or even tertiary changes, already being present, might not be expected to be influenced by any therapy.

ERT

- In several clinical trials ERT has shown to effectively improve the visceral and hematological domains and other disease parameters (e.g., chitotriosidase) in GD1 within a short period.
- The response to ERT of bone disease in adult patients with GD is considered to be much slower.

- In other studies a reduction of bone pain and bone crisis could also be seen within a short time and further decreases of these symptoms could be observed during 2 years of ERT.
- Correlating with the reduction of theses symptoms, ERT showed to have a significant positive effect on the quality of life in GD patients with bone disease after 2 years of treatment.

- However, compared with the rapid reduction of bone pain and bone crisis, morphologically associated changes were seen only after longer periods of therapy.
- Improvements on MRI were seen at the earliest after 2–3 years of treatment, whereas in another study a decrease in bone marrow accumulation of glucocerebroside and increase of BMD was seen only after 3–4 years of ERT.

- Higher ERT doses (80 U/kg/4 weeks) demonstrated a more pronounced and quicker response of bone marrow involvement according to MRI as compared to lower ERT doses (15–30 U/kg/4 weeks).
- A marrow response to ERT may be dependent on the initial size of the spleen prior to therapy.

- GD patients not treated with ERT showed a decreased BMD of about 1SD below the reference population remaining unchanged over time.
- Patients receiving ERT revealed a slow improvement of BMD with greater BMD increases in those patients treated with higher ERT dosages.
- After 8 years of ERT the BMD approached that of the reference population.
- Based on these results normal age- and sex matched BMD seems to be achievable over many years for GD patients when on ERT.

- In pediatric patients ERT improved bone mineral density (BMD) and growth rates and a resumption of growth could be demonstrated.
- In a large cohort study of 884 children on long-term ERT the median height approximated that of the normal population after 8 years of therapy.
- No further bone crisis occurred after 2 years of ERT, and BMD normalized after 6.6 years of ERT.

- On the contrary, Drelichman et al. reported on interruption of ERT for 15–36 months in children leading to recurrence of splenomegaly, hepatomegaly, worsening of blood count, growth retardation, and serious bone manifestations that did not resolve after restart of ERT.

- In summary, in the short term patients on ERT should have a rapid resolution of bone crisis and improvement in bone pain.
- In the long term ERT appears to increase bone mineral density and decreases bone complications.

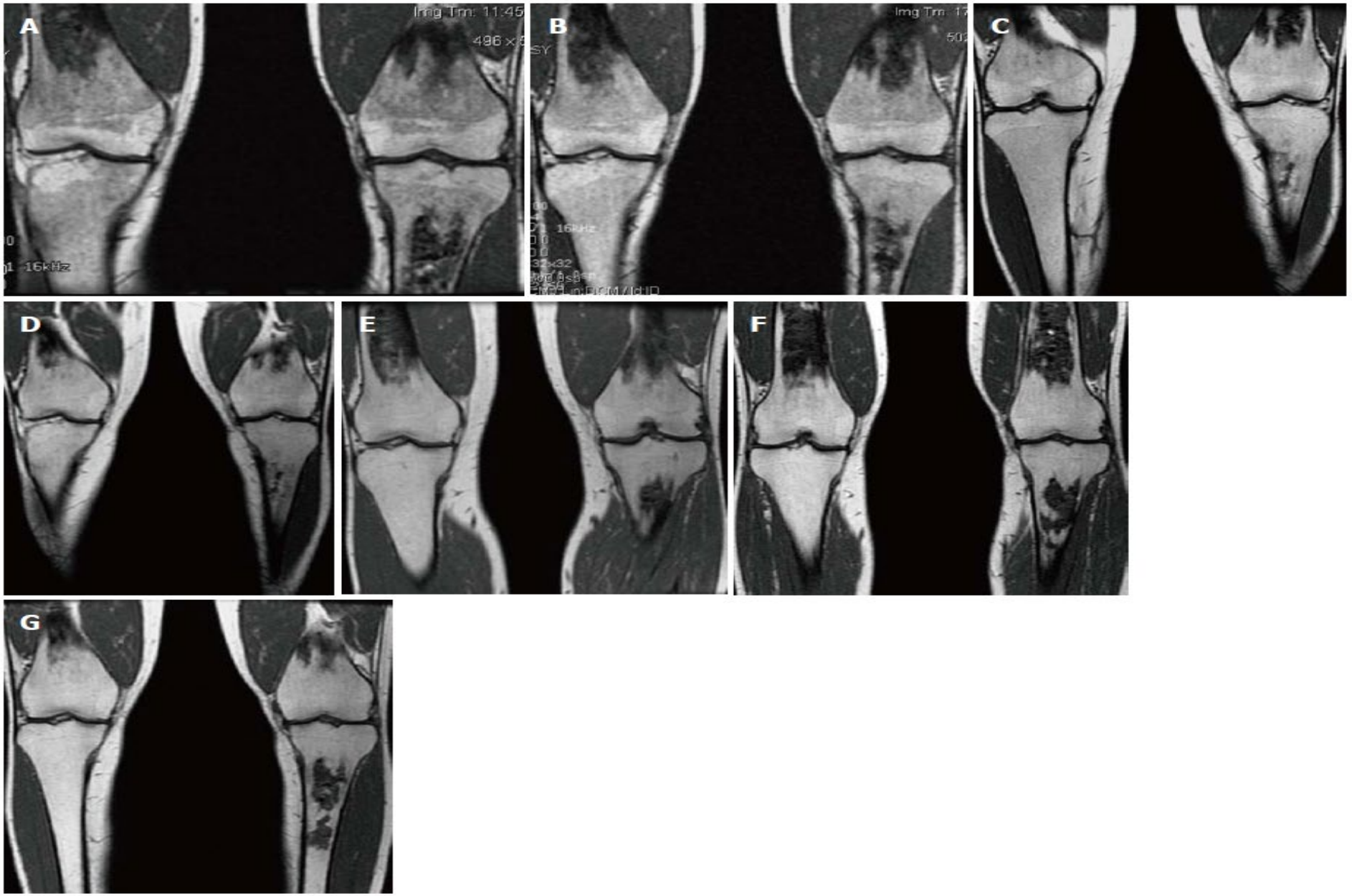

Figure 15 Bone marrow improvement. Gaucher Type 1 patient with N370S/N370S genotype who started enzyme replacement therapy (ERT) in 1997. Coronal T1 WI of the distal femora and proximal tibiae in 1998 (A), 1999 (B), 2002 (C), 2003 (D), 2006 (E), 2008 (F) and 2011 (G). Medullary infarcts are partially seen in both distal femurs and the left tibia. The low T1 SI significantly improves between 1998 and 2002 with near normal marrow signal seen in the noninfarcted areas in 2008 and years later. Although this patient has the same genotype as the patient in Figure 14, there is a longer time to improvement indicating the limited genotype/phenotype correlation.

SRT

- After initial ERT, SRT has also demonstrated to be an effective therapeutic approach in the way that organomegaly was reduced and hematological parameters improved or remained stable.
- Results regarding the effects of SRT on bone disease in GD1 are limited so far.
- Similar to ERT, SRT also showed a positive effect on bone pain and bone crisis.
- After 12 months of SRT no bone pain or any new bone crisis was observed.

- Based on these still limited data, it seems that SRT with miglustat exhibits a rapid positive action on bone pain, the occurrence of bone crisis, and the severity of bone manifestations in GD1.
- The underlying mechanism of miglustat on bone manifestation in GD may be due to its good penetration ability into bone and bone marrow cavity, as miglustat is a small molecule, and its effects on osteoclastogenesis.
- Overall miglustat seems to be a therapeutic alternative for the therapy of bone disease after initial therapy with ERT.

Bone specific therapy

- Several drugs are currently available for the treatment of osteoporosis including oral and intravenous bisphosphonates, hormone replacement therapy, raloxifene, calcitonin, strontium-ranelate, and 1–34 and 1–84 parathyroid hormone.
- In GD patients with osteopenia or osteoporosis additional bone-specific therapies may be applied besides disease-specific therapy with either ERT or SRT.

- Besides the positive effects o bisphosphonates on bone density, no data on fracture risk reduction are available for GD patients.

- Osteonecrosis, in GD most commonly affecting the femoral head (Fig. 8), but also other sites such as the proximal humerus and vertebral bodies, is one of the severest bone complications of GD.
- In this respect, the possible side effect of bisphosphonate-related osteonecrosis of the jaw (ONJ) has to be considered with particular interest in GD.

- Several risk factors have been identified for the occurrence of ONJ including head and neck irradiation, trauma, periodontal disease, local malignancy, chemotherapy, glucocorticoid therapy, age >60 years, and female sex.
- Also dental surgery or tooth extraction have been identified as additional risk factors.
- According to literature, no cases have been reported of ONJ in GD-1 patients on bisphosphonates so far.

- Other specific osteoporosis therapies are not reported in GD patients so far, although they are also potentially applicable.
- With respect to the pathological changes of bone turnover in GD with both increased bone degradation and impaired bone formation, osteoanabolic drugs such as parathyroid hormone or strontium ranelate may be of particular use in GD patients, a circumstance that will have to be evaluated in further studies.

- So far, no specific recommendations are available for GD patients concerning the use and the amount of dosage of calcium and vitamin D.
- Schiffman et al. found calcitriol ineffective in increasing BMD in splenectomized GD patients .
- Recent data suggest that vitamin D deficiency is widely prevalent in GD.

- These results should highlight increased attention to possible vitamin D deficiency in GD-1 patients.
- In order to optimize care of bone disease in GD patients, treatment with calcium and vitamin D, has to be recommended also for GD patients with osteopenia or osteoporosis.
- Frequent evaluation of vitamin D levels will help to evaluate whether the treatment goal of vitamin D sufficiency with 25 (OH)D >75 nmol/L (30 ng/mL), as defined by many vitamin D experts, has been achieved.

Orthopedic interventions

- GD-patients may necessitate orthopedic surgery for bone complications due to bone infarcts, avascular necrosis, or fractures (e.g., to prevent paraplegia after vertebral compression fracture or to protect mobility).
- However, it has to be mentioned that orthopedic interventions in GD patients are associated with increased bleeding complications and loosening of replacement due to the underlying disorder.

- Avascular necrosis, most frequently seen within the hip in GD, places a great disease burden leading to progressive destruction of the affected joint.
- In particular in case of hip involvement consequent immobility will have a significant impairment and effect on quality of life for the patient.
- Total hip arthroplasty may be performed to restore joint function.

- Lebel et al. investigated the effects of hip drilling for juxtaarticular osteonecrosis at a pre-collapse stage in young GD patients.
- The authors found equally poor results in those patients with and without drilling, thus concluding that drilling seems to have no beneficial outcomes for GD patients.

Influence of splenectomy on bone disease

- Before ERT was available splenectomy was the only method to improve the disease status in patients affected with severe cytopenias, functional hypersplenism, or local mechanical pressure due to extensive splenomegaly.
- However, in the long term splenectomy has a negative effect on the course of bone involvement in GD.

- Using BMB scores, splenectomized GD patients had higher BMB scores indicative of severe bone disease than non-splenectomized patients.
- Besides severe bone diseases splenectomized GD patients also revealed bone manifestations more progressive over time compared with GD patients without splenectomy.

Conclusion

- Bone disease in GD consists of complex pathological changes of bone and bone marrow.
- Progressive and irreversible changes to bone, bone pain, and fractures are high burdens for the affected patients and reduce their quality of life.
- Early detection and monitoring of the extent of bone disease by various imaging modalities, preferentially MRI, give the basis for therapeutic decision making.

- As ERT and SRT have shown positive effects in association with bone disease, in particular rapid reduction of bone pain, frequency of bone crisis, and overall improvement in quality of life, therapy should be applied as early as possible.
- Other therapeutic options such as therapy with bisphosphonates may be beneficial, although data are limited for GD.
- All in all, further efforts have to be made to better understand the complex pathologies of bone disease in GD.

- Ng et al. [96] recently hypothesized that additional calcium phosphate cement, which is already widely used in stabilization of fractures, in conjunction with standard decompression of the osteonecrotic femoral head may prevent joint collapse.
- The additional application of calcium phosphate cement may also place a new possibility in the treatment of avascular hip necrosis in GD, although this needs to be studied in the future.

Minimum recommended initial assessment and monitoring recommendations for patients with nonneuronopathic Gaucher disease

Initial assessment and ongoing monitoring	Frequency*	
	Not receiving ERT	Receiving ERT, has not achieved goals
Physical examination		
	Every 6 months	Every 6 to 12 months
Blood tests		
Hemoglobin	Every 12 months	Every 3 months
Platelets	Every 12 months	Every 3 months
Chitotriosidase, PARC/CCL18, HDL	Every 12 months	Every 3 months
Beta-glucosidase and mutation analysis		
Antibody sample¶	Not necessary	Optional sample after 6 months of therapy
Serum immunoelectrophoresis△	Every 12 to 24 months in patients >50 years	Every 12 to 24 months in patients >50 years
Radiographs		
Visceral		
Spleen volume (MRI or US)	Every 12 to 24 months	Every 12 months
Liver volume (MRI or US)	Every 12 to 24 months	Every 12 months
Skeletal		
MRI		
Spine (sagittal T1-weighted)△	Every 24 months, or less frequently if consistently normal	Every 12 months
Femora (coronal T1- and T2-weighted)	Every 24 months, or less frequently if consistently normal (T1- and T2-weighted)	Every 12 month (T1- and T2-weighted)
Plain radiographs◇		
Children: Pelvis, long bones, spine§	Every 12 to 24 months	Every 12 months
Adult: Lateral spine; AP of entire femora¥	Every 12 to 24 months	Every 12 months
DXA spine and hips	Every 12 to 24 months in adults	Every 12 months
Cardiopulmonary		
Children:		
Forced vital capacity	Repeat if abnormal at baseline or if symptoms develop	Repeat if abnormal at baseline or if symptoms develop
Peak expiratory flow rate		
High-resolution chest computed tomography		
Echocardiography		
Electrocardiogram		
Adults (>18 years):		
Electrocardiogram	Every 12 to 24 months for those with borderline or above normal pulmonary pressures at baseline Consider repeating every 2 to 3 years if baseline is normal	Annual evaluation if signs/symptoms of cardiopulmonary disease are present
Chest radiograph		
Doppler echocardiogram (right ventricular systolic pressure)		
Other		
Pain	Every 12 months	Every 6 to 12 months
Quality of life	Every 12 months	Every 12 months
Validated disease severity score	Every 12 months	Every 12 months
Additional tests‡		
White blood count, prothrombin time, activated partial thromboplastin time, iron, iron-binding capacity, ferritin, vitamin B12, aspartate aminotransferase, and/or alanine aminotransferase; alkaline phosphatase; calcium, phosphorous, albumin, total protein, total and direct bilirubin; hepatitis profile, serum immunoelectrophoresis		

ERT: enzyme replacement therapy; PARC/CCL18: pulmonary and activation-regulated chemokine/chemokine (C-C motif) ligand 18; HDL: high-density lipoprotein; MRI: magnetic resonance imaging; US: ultrasonography; DXA: dual-energy x-ray absorptiometry.

* The entire assessment should be performed at baseline and every 12 to 24 months in patients who are receiving ERT and have achieved therapeutic goals. DXA should be performed every 24 months in these patients. The entire assessment also should be performed at the time of dose change or the development of a significant complication.

¶ To be stored and tested only if clinically indicated.

△ Only in children.

◇ Sites not included here should be evaluated if symptoms develop.

§ Plain radiographs of the spine only when patient is symptomatic (eg, back pain), disease is severe, there is poor growth, or kyphosis.

¥ Optional in absence of new symptoms or evidence of disease progression.

‡ Additional tests to be considered and followed appropriately depending upon patient's age and clinical status.

Data from:

1. *Grabowski GA, Andria G, Baldellou A, et al. Pediatric nonneuronopathic Gaucher disease: presentation, diagnosis and assessment. Consensus statements. Eur J Pediatr 2004; 163:58.*
2. *Baldellou A, Andria G, Campbell PE, et al. Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring. Eur J Pediatr 2004; 163:67.*
3. *Charrow J, Andersson HC, Kaplan P, et al. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. J Pediatr 2004; 144:112.*
4. *Weinreb NJ, Aggio MC, Andersson HC, et al. Gaucher disease type 1: revised recommendations on evaluations and monitoring for adult patients. Semin Hematol 2004; 41:15.*
5. *Rosenbloom BE, Weinreb NJ, Zimran A, et al. Gaucher disease and cancer incidence: a study from the Gaucher Registry. Blood 2005; 105:4569.*

Table 2 Organ-wise Involvement in Gaucher Disease.

Organ system	
General	Reduced quality of life, delayed milestones, growth retardation, pubertal status
Skeletal	Chronic bone pain (33%), acute bone crises (7%) Kyphosis including gibbus, scoliosis and chest deformities Bone fractures (7%) Skeletal growth retardation (36%) Bone remodeling failure (Erlenmeyer flask deformity) Osteopenia (55%) Osteonecrosis, avascular necrosis head femur Osteolysis, osteosclerosis
Visceral organs	Abdominal pain, early satiety, feeling of fullness, diarrhea Splenomegaly (85%), splenic infarcts Hepatomegaly (63%) (may progress to cirrhosis, portal hypertension) Cholelithiasis
Hematological	Anemia (34%)—Fatigue, exertional dyspnea, need for blood transfusions Thrombocytopenia (68%) spontaneous bleeding—epistaxis, bruising, menorrhagia or hemostatic problems after trauma, surgery or post-partum bleeding Leukopenia: increased risk of infection Gammopathy
Lungs	Dyspnea (exertional), cough, recurrent respiratory infections Pulmonary hypertension with dyspnea on exertion or at rest, syncope Hepatopulmonary syndrome—clubbing, cyanosis, orthopnea
CNS (Type 2/3)	Strabismus, saccade initiation failure, supranuclear gaze palsy, slow object tracking, hypertonia, rigidity, opisthotonus, bulbar palsy, seizures, ataxia, myoclonus, dementia, mental retardation
Skin	Yellow/brownish discoloration Bruises, petechiae
Heart	Valvular calcification, congestive heart failure, arrhythmias
Eyes	Pingueculae Corneal opacities Strabismus, saccade initiation failure (ocular motor apraxia) in type 3 disease
Lymphatic	Enlarged lymph nodes
Malignancies	Increased risk of multiple myeloma, hematological malignancy, hepatocellular carcinoma, renal cell carcinoma

Table 3 Diagnosis, Work Up and Therapeutic Monitoring in Gaucher Disease (Modified from Niederau, et al[55]).

Type 1—non-neuronopathic form	
Diagnosis and work-up	• Clinical examination (height, weight, liver, spleen size, growth) • Glucocerebrosidase activity in leukocytes (or fibroblasts)—gold standard for diagnosis • Gene mutations (for confirmation, prognosis) • Supportive—laboratory tests: Blood counts, liver function tests, biomarkers—chitotriosidase. If chitotriosidase not available—CCl8, ferritin, TRAP, or ACE • USG/MRI abdomen: liver and spleen size, spleen infarcts, lymph nodes, portal hypertension • MRI of the lower limbs or lumbar spine/other bones if needed • If suspected: X-ray chest, echocardiography for pulmonary hypertension
Initial monitoring	• Every 3 months: clinical examination, growth measurement in children, blood counts • Every 6 months: SF-36 for quality of life, Biomarkers, ultrasound abdomen, and skeletal X-rays, LFT, PT, PTT if needed, DEXA scan • Every 12–18 months: if bone involved—MRI bones
Long-term treatment	• Every 6 months: clinical examination, blood counts, ultrasound abdomen, skeletal X-rays, SF-36 for quality of life, LFT if needed • Every 12 months or in case of problems: biomarkers, DEXA scan • Every 3–4 years: MRI in the presence of bone changes
Neuronopathic forms (type 2 and 3): Initial and follow up tests as appropriate for clinical status	
• Clinical neurological examination • Examination of eye movement (gaze apraxia) • Neuro-ophthalmological investigation, including direct ophthalmoscopy • Measurement of peripheral hearing (electro-acoustical emission in small children, pure tone audiometry in older patients) • Psychological examination which is age appropriate in older children • MRI brain, EEG, brain stem evoked responses • IQ testing	

Item	Median (1: disagree to 9: agree)	% consensus	Result
Monitoring of visceral parameters			
For visceromegaly follow-up, an US exam is enough.	7	51.7	Undetermined[a]
For visceromegaly follow-up, using MRI is recommended.	8	70.5	Agreement
For splenomegaly and hepatomegaly follow-up, an annual US exam is recommended in order to delay the CT/MRI scan to 24–36 months.	8	69.3	Agreement
In the follow-up of stable patients, an echocardiogram every 2 years is recommended.	8	76.1	Agreement
Monitoring of bone disease			
Conventional radiograph is useful for routine monitoring.	3	71.6	Disagreement
Conventional radiograph is only useful in the follow-up if the patient shows clinical signs suggestive of bone manifestations.	7	70.1	Agreement[a]
In the follow-up of patients with bone pain or active bone disease, an MRI should be performed every 6 months.	7	55.2	Undetermined[a]
In the follow-up of patients with bone pain or active bone disease, an MRI should be performed every 12 months.	8	71.3	Agreement[a]
Bone symptoms should be assessed by densitometry and MRI (lumbar, femoral, hip, and symptomatic areas).	8	93.2	Agreement
In the follow-up of patients with bone pain, CT can be a suitable exam if MRI is not available.	8	75.0	Agreement
A radiologist trained in GD pathology is recommended for both MRI and radiograph interpretation.	9	100	Agreement
The use of pain questionnaires is recommended to monitor bone involvement.	9	93.3	Agreement
The amount of painkillers taken between visits should be considered to assess the degree of pain.	9	95.5	Agreement
In the follow-up of patients with chronic bone pain, determination of blood parameters of inflammation (ferritin and/or ESR and/or CRP) is advisable.	8	74.2	Agreement
In the follow-up of patients with bone pain, a differential diagnosis with neuropathic pain is recommended.	8	87.6	Agreement
Follow-up of patients with bone symptoms should be the same for patients with and without prostheses.	5	23.0	Discrepancy[a]
In the follow-up of patients with bone symptoms and prostheses, CT is recommended.	7	57.5	Undetermined[a]
Follow-up of patients with joint prostheses should include an orthopedic surgery specialist, who may be part of the team.	9	96.6	Agreement
For patients with joint prostheses suffering pain in the prosthetic joint area or presenting signs of infection or loss of function, a scintigraphy and a visit to the orthopedic surgery specialist is recommended.	9	95.5	Agreement
For the assessment of pain and functional status, comparing the need for painkillers between visits is recommended.	8	95.5	Agreement
The SF-36 questionnaire is useful for routine follow-up of the GD patient.	7	70.8	Agreement
The SF-36 questionnaire is recommended for monitoring functional status and pain.	8	77.0	Agreement[a]
The SF-36 questionnaire is only useful in the follow-up of the GD patients included in clinical trials.	3	56.3	Undetermined[a]
The SF-36 questionnaire can be given to the patient for completion at home and can be collected during the next doctor visit, at least once a year.	8	78.7	Agreement