

Denosumab and surgery for the treatment of Perthes' disease in a 9-year-old boy: favorable course documented by comprehensive imaging— a case report

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A boy aged 9 years and 4 months developed a recurrent right-sided limp. His father, a radiologist, prompted a contrast magnetic resonance imaging (MRI) after 6 weeks and diagnosed early Perthes' disease (Figure 1).

There were risk factors for a poor prognosis. The boy was relatively old for Perthes' disease. He was a physically active child of small stature with uncertain compliance for non-weight bearing. Disseminated epiphyseal signal alterations in MRI suggested total involvement, Catterall group 4 (Catterall 1971). 2 weeks later, a posteromedial epiphyseal-metaphyseal cyst was seen. At a new examination another 2 weeks later, radiographs and MR images showed a subchondral fracture, but the epiphysis was not sclerotic (Figure 2). The disease was

in early stage Ia according to the modified Waldenström classification (Joseph et al. 2003, Hyman et al. 2015).

Owing to the risk of a severe course, we suggested early containment surgery. The family, however, opted for a mainly conservative treatment with close follow-up by MRI.

Thus, treatment consisted of minimal weight bearing by use of crutches or a wheelchair.

At 5 months after onset, there was still no sclerosis or significant extrusion in radiographs. However, a slight reduction in epiphyseal height and some anterior flattening indicated stage Ib. The subchondral fracture now involved slightly more than 50% of the epiphysis. A simultaneous contrast MRI showed complete lack of perfusion in the center, a small area of hyperperfusion laterally, persistence of the epiphyseal-metaphyseal cyst posteromedially, and marked synovitis (Figure 3), all suggesting a worsening hip. The family decided to resort to anti-resorptive treatment. A dose of 60 mg denosumab was administered.

At 11.5 months, an MRI showed stage IIb with signs of beginning of loss of containment (Meiss 2001) (Figure 4). We strongly advised surgery. Further application of denosumab was not considered. 1 year after onset and 7 months after the denosumab injection, radiographs showed atypical re-ossification with a centrolateral density (stage IIIa), moderate extrusion, a faint, radiolucent metaphyseal band, and major anterior flattening (Figure 5). 1 month later, a varus osteotomy of the

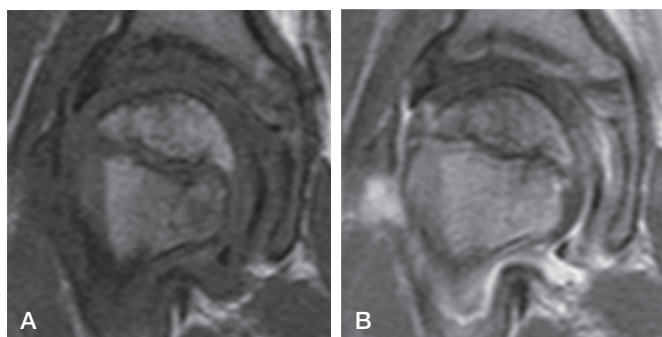


Figure 1. At 6 weeks. MRI (A) and contrast MRI (B). Prior to stage Ia.

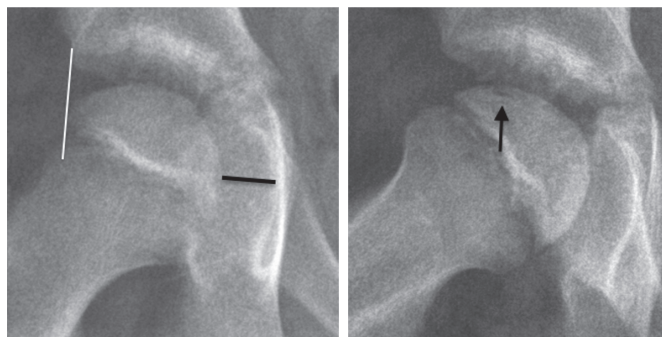


Figure 2. At 2.3 months. Start of extrusion. Subchondral fracture. Early stage Ia.

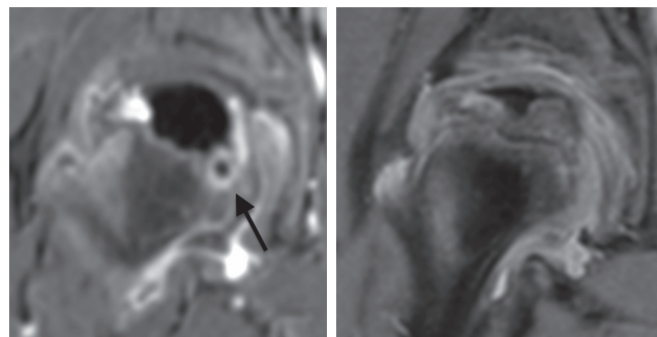


Figure 3. At 5.2 months. Contrast MRI. Cyst. Stage Ib. 2 days later, denosumab was administered.

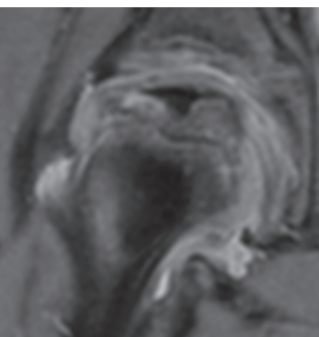


Figure 4. At 11.5 months. PD-weighted MRI. Beginning of loss of containment. Stage IIb.

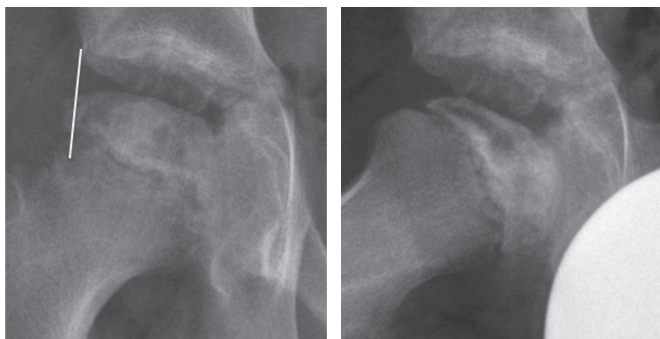


Figure 5. At 1 year. Moderate extrusion. Anterior flattening. Stage IIIa. A proximal varus osteotomy was performed 1 month later.

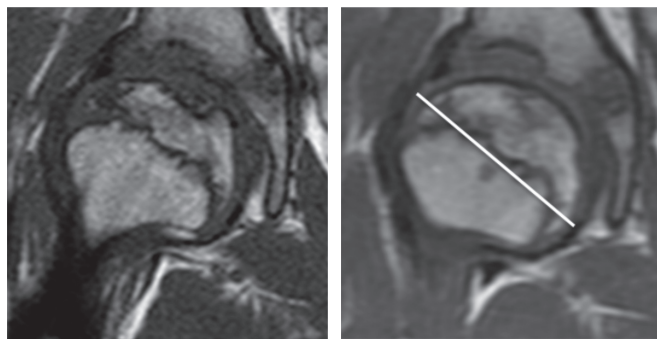


Figure 7. At 2 years. 90% re-ossification. Stage IIIb.

Figure 8C. At 2 years and 8 months. An 11% increase in the maximum diameter. Almost stage IV.

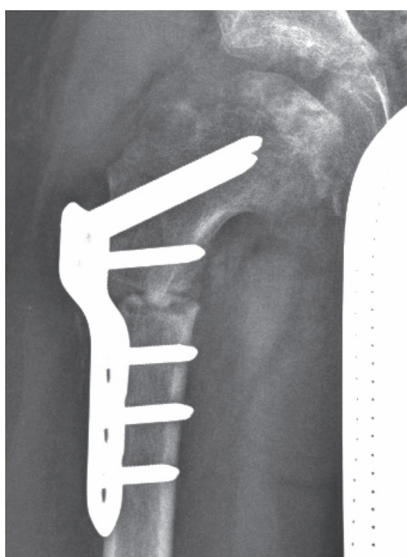


Figure 6. Six weeks postoperatively.

proximal femur was performed. 6 weeks postoperatively, the contour of the head was uneven and the bone texture irregular, possibly attributable to the denosumab therapy (Figure 6).

Radiographs 6 months postoperatively revealed consolidation of the osteotomy; 1 month later, the plate was removed.

2 years after onset, MRI showed an enlarged, slightly ovoid, well-contained head with advanced re-ossification (stage IIIb) (Figure 7).

The last MRI, performed 2 years and 8 months after onset, showed healing with about 90% re-ossification (almost stage IV). The head was almost spherical (Figure 8A–E, see Supplementary data). There was an 11% increase in the maximum diameter (Figure 8C). Under the assumption of bilateral sphericity, the volume was 60 cm³ on the right side and 44 cm³ on the left side. The difference would mean an increase in volume of 36%.

In the final assessment, the boy could comfortably carry out his daily activities and sports. He had normal hip motion and no pain or limp.

The boy’s parents consented to data from the case being published.

Discussion

In principle, Perthes’ disease is self-healing, and the optimal outcome is a normal hip (Stulberg et al. 1981). However, deformation during the course of the disease leads to a high risk of later osteoarthritis.

Treatment of Perthes’ disease varies between supervised neglect, strict non-weight bearing, and surgery. The cause of the disease still being unknown there is no cause-focused therapy. In his recent review, Kim (2012) reported that increased bone resorption and delayed new bone formation, in combination with continued mechanical loading of the hip, contribute to the femoral head deformity. Thus, biological treatment appears possible.

Suppression of osteoclastic activity using intravenous biphosphonate in experimentally induced femoral head necrosis in piglets seemed to prevent total head collapse (Kim et al. 2005). This approach was further analyzed in clinical trials—with variable results (Agarwala et al. 2005, Young et al. 2012, Lee et al. 2015). Treatment with bisphosphonates has limitations, especially in children. Bisphosphonates accumulate in bone and may remain incorporated for years. Animal studies have shown that bisphosphonates can cause impairment of long bone growth (Lepola et al. 1996, Camacho et al. 2001, Kim et al. 2005).

As for denosumab, a human monoclonal antibody to RANKL that also acts as an inhibitor of osteoclasts, no growth retardation has been noted in animal or clinical studies (Kim et al. 2006, Wang et al. 2014, Kobayashi and Setsu 2015). Denosumab has the advantage of not binding to bone. Denosumab treatment rapidly reduces bone turnover, reaching a nadir by 3 days. Return of turnover to pretreatment level generally occurs within 9 months. Caution should be exercised regarding the off-label use in children because of the risk of initial severe hypocalcemia. The blood level of vitamin D should be kept in the high normal range, and sufficient intake of calcium is needed (Grasemann et al. 2013, Hoyer-Kuhn et al. 2016)—recommendations that we respected. On the other hand, there

is a risk of rebound hypercalcemia. The latter is caused by a washout of calcium after discontinuation of the drug and can result in renal dysfunction. Close monitoring and treatment is essential (Wang et al. 2014, Setsu et al. 2016).

Denosumab could probably interfere with fracture healing. In an animal model, a delay in callus remodeling was noted, but also an increase in callus strength and stiffness (Gerstenfeld et al. 2009). Because no major negative clinical effects have been shown to date, osteoporosis therapy with denosumab is not interrupted if a fracture occurs (Adami et al. 2012). However, some recent reports on atypical femoral fractures in patients receiving denosumab underscore the need for future epidemiological studies (Aspenberg 2014, Schilcher and Aspenberg 2014).

With these precautions in mind, Hoyer-Kuhn et al. (2016) used denosumab in a group of children suffering from severe osteogenesis imperfecta and showed that the subcutaneous application of 1 mg per kg body weight every 12 weeks was efficient and safe. In our case, a single dose of 1.94 mg per kg body weight was administered.

There is increasing experience with the use of denosumab in severe disorders in childhood such as aneurysmal bone cyst, juvenile Paget's disease, giant cell tumor of bone, fibrous dysplasia, and osteogenesis imperfecta (Lange et al. 2013, Grasemann et al. 2013, Kobayashi and Setsu 2015, Wang et al. 2014, Hoyer-Kuhn et al. 2016).

In our case, evaluation of the early response to the drug was difficult. As there was no rapid improvement in joint morphology, we recommended surgery. With earlier administration of denosumab, surgery might perhaps have been avoided.

In retrospect, the effect of the drug resembles the effect of an osteoplasty. Wang et al. noted that denosumab treatment in a child with fibrous dysplasia led to retention of primary spongiosa of the growth plate of the distal tibia. We hypothesize that this phenomenon is ubiquitous, and occurs also at the circumferential growth zone of the proximal femoral epiphysis (Kim et al. 2012, p 663). Hence, denosumab might have led to preservation of epiphyseal trabeculae with osteogenic capacity.

To our knowledge, this is the first report of treatment of Perthes' disease with denosumab in combination with a varus osteotomy and close follow-up by MRI and radiographs. It is our impression that denosumab had a positive effect on the outcome. It is very unlikely that the good result can be attributed solely to the varus osteotomy which was performed 1 year and 1 month after the start of symptoms. The favorable development is encouraging in that a new orientation in the management of Perthes' disease is possible.

Supplementary data

A chronological overview and figures covering both hips are available as supplementary data in the online version of the article <http://dx.doi.org/10.1080/17453674.2017.1298020>.

No competing interests declared.

ALM wrote the manuscript. FB provided osteological expertise and reviewed the manuscript. KB operated on the patient. GES was the treating physician and kept patient records.

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