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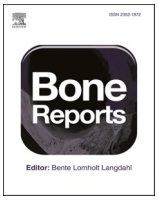

Case Report

Giant cell tumour of bone in os sacrum of a prepubertal girl – Surgical and medical treatment with zoledronate and denosumab

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ABSTRACT

A giant cell tumour of bone presented in the os sacrum of a prepubertal girl. Surgery with reconstruction was performed, but total resection was impossible. Zoledronate failed to avoid tumour regrowth, and treatment was changed to denosumab, despite not being recommended for use in growing children. Denosumab treatment for 21 months reduced and stabilized tumour size, the girl became pain free with asymptomatic side effects as mild hypocalcemia, hypophosphatemia and sclerosis of newly formed bone.

1. Introduction

Giant Cell Tumour of Bone (GCTB) is a locally aggressive, osteolytic neoplasm of bone, usually non-malignant, and rarely metastasizing. GCTB is rare in children and treatment experience thus scarce. When possible, total tumour removal is the curative treatment of choice, but the tumour location may hinder complete surgical removal because of skeletal destabilization and/or invasive tumour growth into vital structures. Following incomplete surgical tumour removal of GCTB, denosumab is the treatment of choice for tumour control in adult patients with mature skeletons (Tsukamoto et al., 2021). Tumour cells in GCTB express nuclear factor-κβ ligand (RANKL) being responsible for its osteolytic behaviour (Borkowska et al., 2022). In this case presentation, we discuss the surgical and medical treatments of a large sacral tumour with invasive growth in a prepubertal girl.

2. Case

An 11-year-old girl presented with lower back pain for six months radiating to left buttock and knee.

2.1. Investigations

MRI revealed deformation of S1 with bony collapse, due to a tumour process protruding 2.5 cm anteriorly and 1.5 cm posteriorly with severe stenosis of the spinal canal, also involving both pars lateralis of os sacrum (Fig. 1a and b). Biopsy revealed large osteoclast-like giant cells with multiple nuclei, establishing the diagnosis of GCTB with no suspicion of giant cell rich osteosarcoma.

2.2. Treatment

The patient underwent surgical removal of tumour masses in S1 with decompression of nerves, ultrasound curettage of cavities, placement of two fibular allograft struts anteriorly between end-plates of L5 and S2, allograft transplantation in the large lateral resection cavities, screw/rod-stabilization from L4 to os Ileum bilaterally, and finally postero-lateral intertransverse bone transplantation.

Post-surgery pain was treated with paracetamol 375 mg four times per day, and oxycodone, extended release, 5 mg three times per day (body weight 31 kg). Oxycodone was tapered over six weeks and

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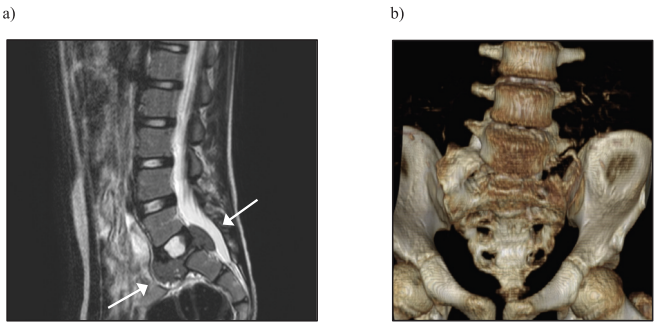

Fig. 1. MRI and CT at presentation.
a) MRI with deformation of S1 and bony collapse (pointing arrows), due to tumour masses protruding 2.5 cm anteriorly and 1.5 cm posteriorly, causing severe stenosis of the spinal canal. b) CT of the sacral region reveals tumour with invasive growth with destruction of both pars lateralis of os sacrum.

paracetamol over eight weeks post-surgery and dosed as required thereafter. Neuropathic pain due to nerve compression was treated with amitriptyline 10 mg two times per day, and pregabalin 25 mg three times per day. After gradual tapering, amitriptyline was ceased five months and pregabalin eight months post-surgery. Pain medication was adjusted according to observations provided by the parents.

As total tumour removal was impossible (Fig. 2a), medical treatment with an anti-resorptive treatment was needed for controlling growth of the tumour remnants and ensuring healing. Zoledronate treatment of 2.5 mg every 4 weeks (0.08 mg/kg), was initiated as half of the recommended adult dose (Dubey et al., 2019). A dental examination was performed before starting zoledronate treatment with no findings of concern regarding the potential risk for developing osteonecrosis of the jaw. After zoledronate infusions, asymptomatic hypocalcaemia was present with the lowest value of p-ionized calcium of 1.09 mmol/l (normal range 1.18–1.32 mmol/l) on day two after the first dose. Hypocalcaemia was accompanied by increase in parathyroid hormone of 13.7 pmol/l (normal range 2.3–9.3 pmol/l) and hypophosphataemia with a nadir of p-phosphate of 0.81 mmol/l (normal range 1.16–1.81 mmol/l). The 25(OH)2D level before commencing the zoledronate treatment was 86 nmol/l, and according to the zoledronate treatment protocol at our centre, sufficient vitamin D status with p-25-hydroxy vitamin D of >70 nmol/l was ensured by a daily supplementation of vitamin D3 of 19 μg increasing the dose to 38 μg/day during the week before and after zoledronate infusions. As the girl disliked milk, calcium-carbonate tablets provided 1600 mg/day one week before zoledronate, 2400 mg the week after and 800 for the intermediate two weeks. Phosphate supplementation was ensured by chocolate milk during the week after infusion.

Due to tumour expansion 4.5 months post-surgery, treatment was changed from the planned dose of zoledronate to denosumab 70 mg/m^2 every 4 weeks with loading doses on days 8 and 15 of the first cycle. One week after starting denosumab, despite calcium-carbonate 1600 mg/day asymptomatic hypocalcemia with the lowest value of p-ionized calcium of 1.14 mmol/l was corrected by 1.5 μg of activated vitamin D (alphacalcidol) per day. In addition, calcium-carbonate was increased to 1600 mg one week before and after denosumab including 0.25 to 0.5 l chocolate milk, and 1200 mg calcium-carbonate between injections. Before treatment start, the urine calcium-creatinine ratio (Uca/cr) was elevated, 2.59 mmol/mmol (normal range < 0.70 mmol/mmol) but decreased to very low values of <0.3–0.12 mmol/mmol during both zoledronate and denosumab treatment. We suspect the pre-treatment elevated Uca/cr was due to active osteolysis by the GCTB.

A gradual increase in the intervals between denosumab injections,

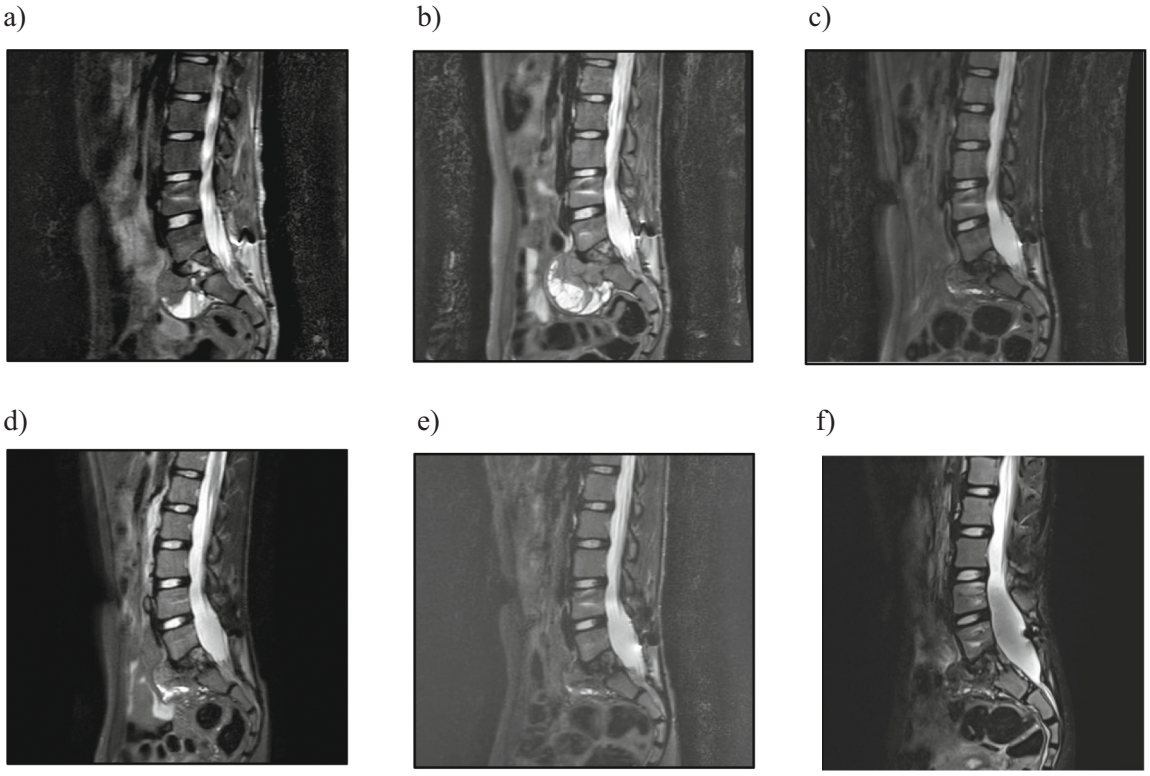

Fig. 2. Changes in tumour size by MRI.
a) One month post-surgery, baseline for zoledronate treatment, tumour volume 47 cm^3, b) four months post-surgery, 2.5 months of zoledronate treatment, tumour volume 153 cm^3, c) six months post-surgery, two months of denosumab, tumour volume 70 cm^3, d) 12 months post-surgery, seven months of denosumab, tumour volume 76 cm^3, e) 15 months post-surgery, 10 months of denosumab, tumour volume 65 cm^3, f) 21 months post-surgery, 16 months of denosumab, tumour volume 78 cm^3.

ensuring continued tumour control has been commenced after 12 treatment cycles (12 months), where the interval between denosumab 70 mg/m^2 was increased from 4 to 6 weeks. Six months after increasing the denosumab interval to 6 weeks, Uca/cr gradually increased to 0.98 mmol/mmol with p-ionized calcium remaining in the mid normal range and p-PTH values low-normal. Alphacalcidol was then reduced to 1.0 μg per day and after nine months further to 0.5 μg per day as p-ionized calcium increased to 1.32 mmol/l, p-PTH was suppressed to 1.1 pmol/l, and Uca/cr remained normal 0.5 mmol/mmol. All bone turnover markers (BMT's) remained stable after increasing the denosumab interval and tapering of alphacalcidol.

2.3. Outcome and follow-up

A multidisciplinary team (MDT) comprising orthopedic spine surgeons, paediatric and adult endocrinologists, paediatric and adult oncologists, and a radiation therapist, was established to develop a follow-up plan for the subsequent medical adjuvant treatment. In addition, radiologists, a specialized dentist, physiotherapists, and a pain therapist were involved in the treatment and care of the patient.

After 3 cycles of zoledronate, the tumour volume (calculated by estimating tumour as the shape of a cylinder) using MRI had expanded from 46 cm^3 to 153 cm^3, thus to approximately three times the size immediately after surgery (Fig. 2a and b), and the BTM's of plasma (p)-bone specific alkaline phosphatase (BSAP) in addition to p-carboxyterminal-crosslinked-telopeotide of type I collagen (CTX) and p-N-terminal propeptide of type I procollagen (PINP) had increased (Fig. 3a and b). Treatment was then changed to denosumab.

Tumour volume was significantly reduced to 70 cm^3 (Fig. 2c) after 2 months of denosumab treatment and remained stationary thereafter (Fig. 3a) with a tendency towards a slight increase in tumour size after increasing the dosing interval at 16 months post-surgery. In addition, BTMs decreased (Fig. 3b). Denosumab treatment greatly reduced pain, where pain relief was reported after three months, and the girl stopped pain medication after four months of denosumab treatment. After eight months of denosumab treatment, she was unrestricted in her movements and physical performance, and pain free.

After 16 months of denosumab treatment, the tumour size remained unchanged (Fig. 3a), but with increasing calcification of tumour by CT at 11 months of denosumab treatment (Fig. 4).

Due to stabilization of the tumour size and calcification of tumour, a gradual increase in intervals between denosumab injections, still ensuring tumour control has been commenced after 12 treatment cycles (12 months). Thereafter the interval between denosumab 70 mg/m^2 was increased to every 6 weeks. At 21 months of denosumab treatment the BTMs remain stable (Fig. 3b). The MRI at 13 months of denosumab treatment (18 months post-surgery) indicates a minor increase in tumour volume compared to MRI at 10 months of denosumab treatment (15 months post-surgery), thus from 65 to 83 cm^3. This may be due to differences in positioning of the child at MRI as tumour volume, but as tumour volume after 21 months of denosumab treatment (24 months post-surgery) was 89 of cm^3 (Fig. 3a), we are aware of a possible true tumour expansion after increasing the dosing interval. The BTMs remained stable after increasing the dosing interval (Fig. 3b).

Pulmonary metastases are reported in 1–9 % (Chan et al., 2015), and we therefore performed chest x-rays every six months, all without metastases.

Growth velocity was unaffected, and height standard deviation (SD) increased from 0 to +0.22 SD during the observation period of 21 months, coinciding that the girl started pubertal development.

A dual-energy X-ray absorptiometry (DXA) scan (Hologic Horizon A, software version 13.6.0.5) was performed after 12 months of denosumab showing a normal areal bone mineral density (aBMD) of 0.863 g/m^2, z-score + 0.5 SD of L1 and L2. Due to artifacts from metal screws/rods, L3 and L4 and total body BMD could not be assessed. At the DXA images, pronounced sclerosis of newly formed bone adjacent to growth plates of the long bones were observed (Fig. 5).

At present, the side-effects noted from denosumab treatment are mild hypocalcaemia, fully corrected by treatment with calcium supplementation and active vitamin D, hypophosphatemia driven by the mild to moderate increase in PTH due to abrupt decrease in calcium post denosumab dosing, and the sclerosis of newly formed bone, all being asymptomatic.

3. Discussion

Total resection of GCTB of the sacrum is often challenging because of tumour surrounding the sacral nerves and vessels, and when total resection is not possible, life-long medical treatment is necessary to control tumour growth (van der Heijden et al., 2015; Chawla et al., 2019; Tsukamoto et al., 2021).

RANKL is a cytokine inducing osteoclast differentiation and activation and thereby bone modelling (primarily of actively growing bone), and remodelling. RANKL plays a central role in GCTB, where overexpression by the mononuclear neoplastic stromal cells recruits multinucleated osteoclast-like giant cells capable of resorbing bone (Borkowska et al., 2022).

Denosumab, a RANKL inhibitor, is a potent inhibitor of osteoclastic bone resorption and expansion of the GCTB and is first choice of treatment in adults with mature skeletons, with non-resectable or metastatic GCTB. At present, denosumab is only indicated in a small number of rare RANKL-mediated disorders in children. Denosumab eliminates the multinucleated osteoclast-like giant cells in GCTB, but the neoplastic stromal cells with a mutation in H3 Histone, Family 3A (*H3F3A*) survive the treatment and show histological alterations (van der Heijden et al., 2015; Kato et al., 2018; Borkowska et al., 2022). In addition, reports showing entrapped neoplastic stromal cells in the solid, circumferential bony layer in the lesion formed during treatment with denosumab may serve the explanation for the potential reactivation and local relapse seen when denosumab treatment is discontinued (Asano et al., 2022).

Preoperative denosumab may downscale the tumour stage and potentially facilitate a less invasive and/or joint sparing surgery (Rutkowski et al., 2015; Traub et al., 2016), but as a recent review reports an increased risk of local recurrence with preoperative denosumab treatment before curettage, preoperative denosumab treatment must be used with caution considering the potential benefits and the risks (Tsukamoto et al., 2021). In addition, as denosumab changes the tumour tissue into a gritty, fibrous-like tissue with areas of new bone, difficulties in determining when resection of all tumour tissue is complete may arise (Traub et al., 2016).

Standard dosing in adults with unresectable GCTB is 120 mg of denosumab every four weeks with additional doses on days 8 and 15 during the first cycle, but investigations of tumour control with increased interval and/or diminished dose are lacking. Unfortunately, the awaited study (NCT03620149) investigating the effect of increasing the interval of denosumab to 12-weekly instead of 4-weekly after 12–15 months of denosumab treatment due to unresectable GCTB, failed in recruiting participants and was therefore terminated ahead of time.

Denosumab may potentially interfere with the in-healing and future vitality of the allografts. In the present case, zoledronate was therefore the primary choice of treatment to control tumour growth in addition to ensure in-healing of the allografts. After three months of treatment with zoledronate, allografts were vital and well in-healed, but the tumour had expanded considerably. We considered the best medical treatment option was to switch to denosumab, which effectively reduced tumour size (Figs. 2 and 3a) and pain. A recent paper evaluating the efficacy of zoledronate vs. denosumab in adult GCTB, found denosumab superior to zoledronate regarding tumour disappearance ($p = 0.032$) in addition to an increased 4-year recurrence free survival rate ($p = 0.035$) (Yue et al., 2022).

Denosumab potentially inhibits bone modelling of the growing skeleton and is therefore not recommended in growing children, and no

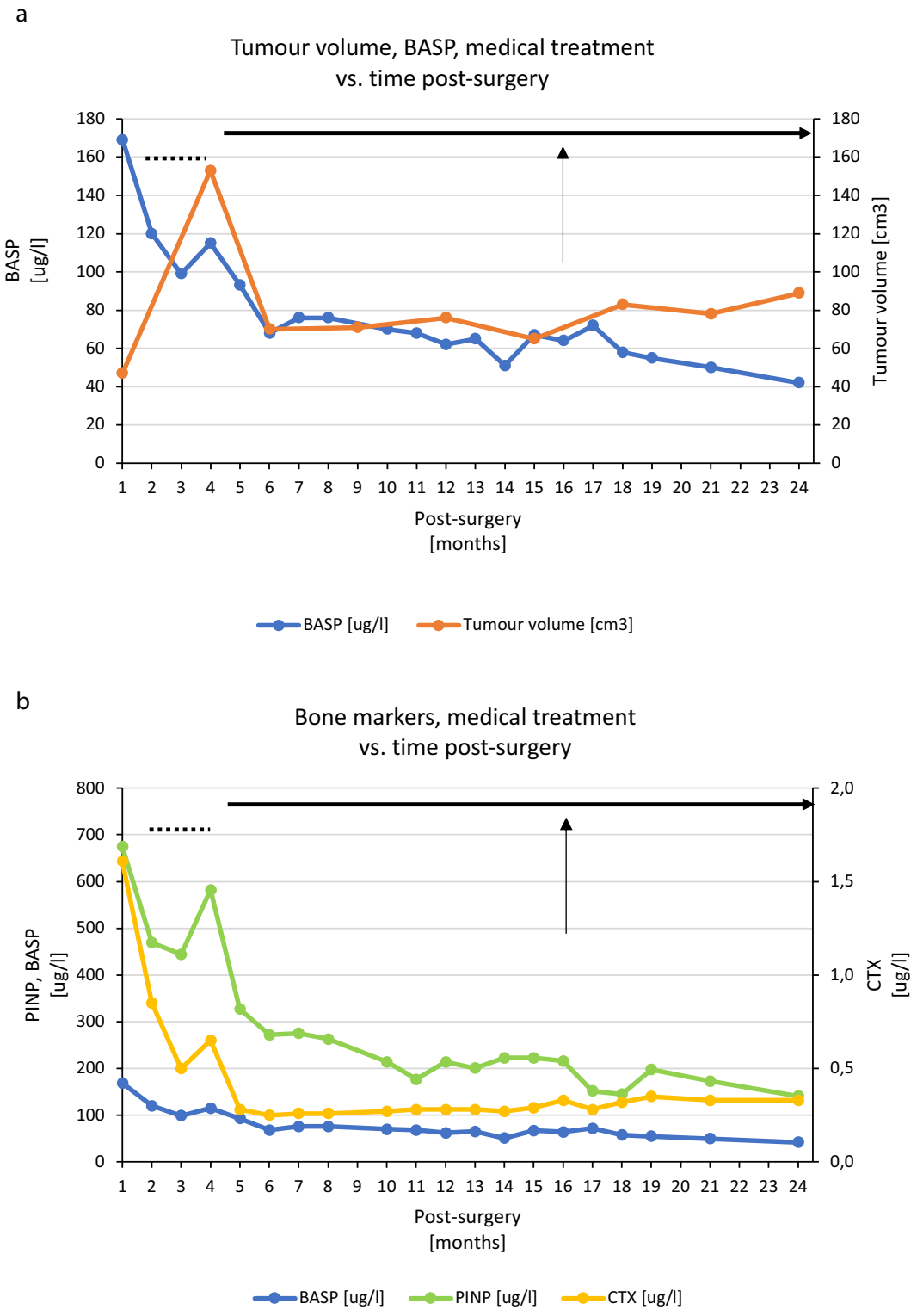

Fig. 3. a. Tumour volume, BASP and medical treatment with zoledronate followed by denosumab vs. time post-surgery.
Arrow at time point for changing denosumab dosing from every 4 to every 6 weeks.
Reference range BASP age 11–14 years: 20.8–172.3 μg/l (Huang et al., 2011)
b. Bone markers; PINP, BASP and CTX vs. time post-surgery.
Arrow at time point for changing denosumab dosing from every 4 to every 6 weeks.
Reference range BASP age 11–14 years: 20.8–172.3 μg/l (Huang et al., 2011); reference range PINP age 11.1–12 years: 65.3–855.8 μg/l (Bayer, 2014); reference range CTX 10–13 years: 0.627–1.955 μg/l (de Melo et al., 2018).

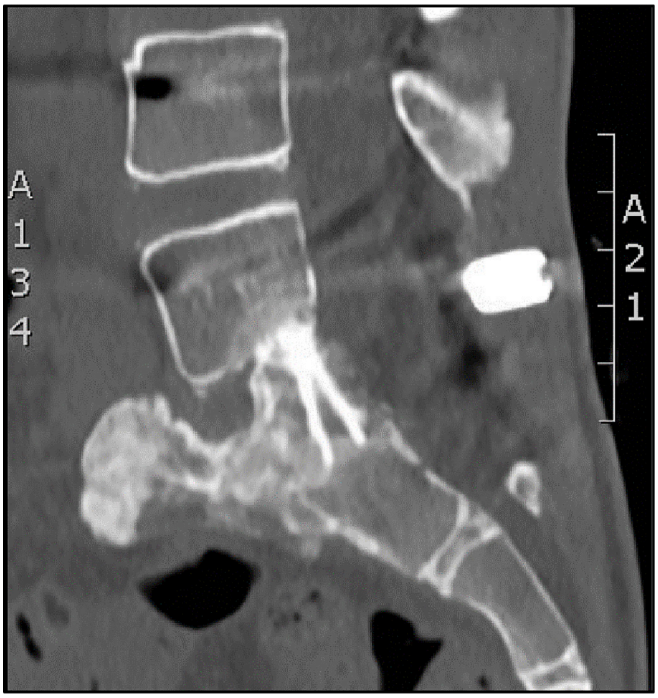

Fig. 4. Tumour calcification by CT 15 months post-surgery, after 12.5 months of medical treatment, of which the first 2.5 months were zoledronate and the following 10 months were denosumab.

consensus on duration, maintenance dose or interval between doses is available. A paper from a tertiary paediatric centre in Australia describes a treatment protocol for central giant cell granuloma (CGCG) in children. The treatment protocol propose denosumab 70 mg/m^2 body surface area on days 1, 8 and 15, then 4-weekly from day 29 (Vanderniet, 2022). We decided to dose denosumab in our case according to this protocol, when zoledronate failed to control tumour growth after 3 treatment cycles.

As the tumour in our case could not be completely resected, lifelong denosumab treatment is expected, but the maintenance dose and optimal treatment interval are currently unknown.

Tapering denosumab dose is warranted to avoid hypermineralization and sclerotic bone as previously reported (Kobayashi and Setsu, 2015), in addition to the non-modelling of growing epiphyses potentially resulting in an Erlenmeyer deformity. It was previously reported that GCTB of the os sacrum in a prepubertal boy was successfully treated with denosumab with subsequent total resection. The boy continued growing at the same rate during and after denosumab treatment but developed asymptomatic sclerotic metaphyseal bands on X-rays (Kobayashi and Setsu, 2015) in addition to severe hypercalcemia four months after the last denosumab treatment (Setsu et al., 2016). Normal growth rates were also described in three children treated with denosumab for CGCG (Vanderniet, 2022).

Severe rebound hypercalcemia from rebound bone modelling and remodelling has been described when tapering as well as stopping denosumab treatment in still growing children, especially at time of high growth velocity as seen during the pubertal growth spurt (Boyce, 2017; Akel et al., 2019; Vanderniet, 2022).

Tartrate-resistant acid phosphatase 5b (TRACP 5b), as a unique

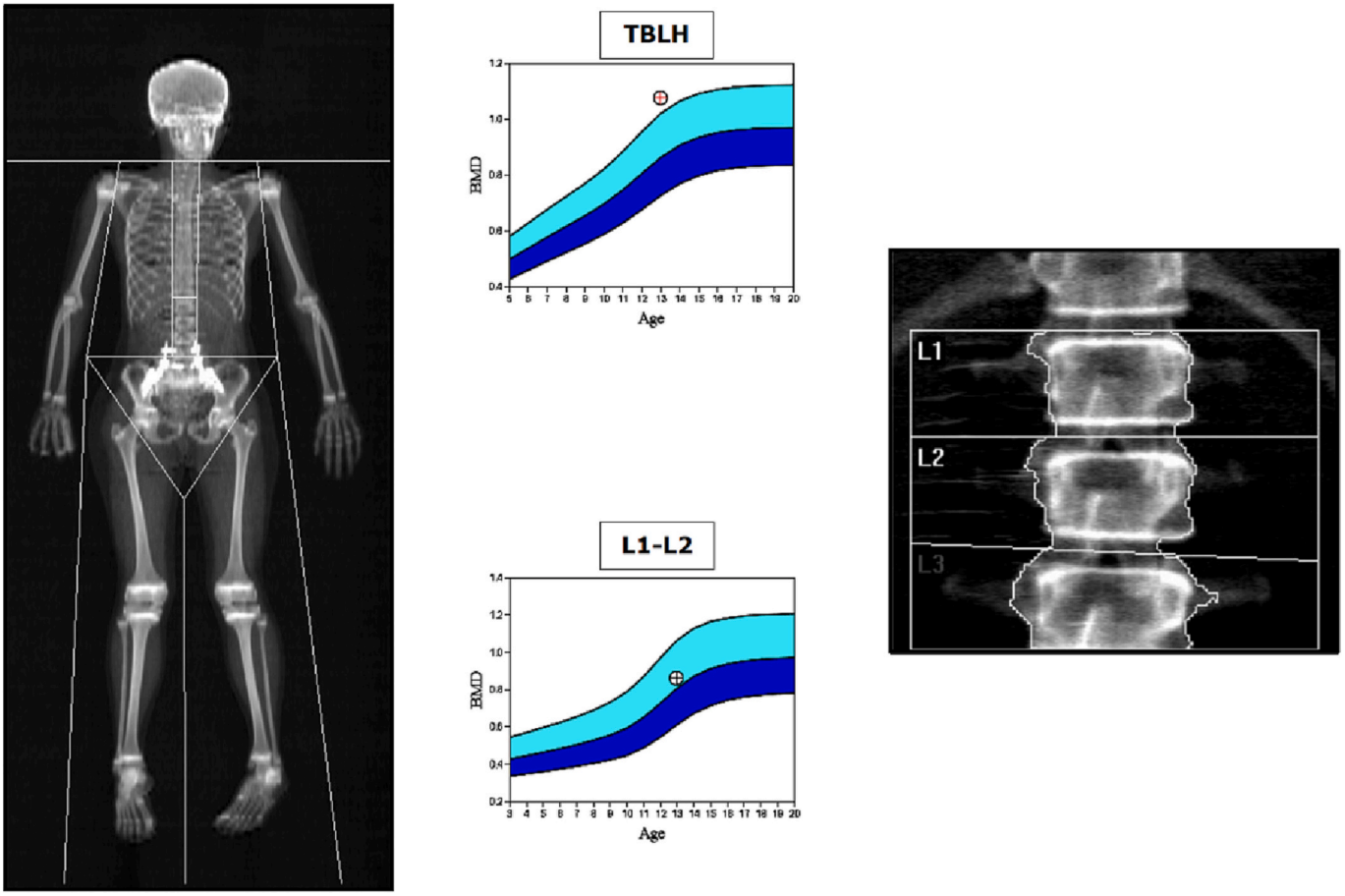

Fig. 5. DXA scan after 12 months of denosumab treatment with normal aBMD of 0.863 g/m^2, z-score + 0.5 SD of L1 and L2. The DXA images reveals pronounced sclerosis of newly formed bone adjacent to growth plates of the long bones and spine.

marker of osteoclast number, has been found useful as a marker for diagnosing GCTB and for detecting recurrence of the tumour (Shinozaki et al., 2012). Unfortunately, TRACP 5b analysis is not a routine analysis in most hospital laboratories. In our case, total alkaline phosphatase was initially measured five weeks post-surgery and was found to be at the upper range of normal, but as the corresponding BSAP was exceeding the upper measurement range of the assay, we suggested BSAP to be a potential marker of GCTB tumour activity. The subsequent samples of BSAP were diluted and fluctuations in BSAP have indeed reflected the changes in tumour size (Fig. 3a). This was also seen for CTX and PINP during 21 months of follow-up (Fig. 3b). A recent paper showed a significant decrease in ALP, CTX and osteocalcin after three months of denosumab treatment in adults with GCTB. Eight cases had unresectable GCTB and 43 underwent surgery after six months of treatment with denosumab, but there was no reporting of changes in BTMs with relapse of tumour despite a median follow-up time of 59 months (Palmerini et al., 2022). As BSAP is readily available in many laboratories and cheap, we suggest BSAP to be a useful marker of tumour growth and activity.

Treatment has been tapered after 12 months of denosumab by increasing the interval between denosumab dosing from 4 to 6 weeks for six months. If no tumour regrowth, we consider increasing the interval to 8 weeks thereafter 24 months of denosumab treatment, while continuing the 70 mg/m^2 dose. This treatment change may increase the risk for tumour growth as well as hypercalcemia. Currently, we monitor tumour size by MRI every three months, fasting measurements of p-ionized calcium, PTH, BSAP, one week before the denosumab treatment, currently being every six weeks. The first signs that may lead the attention to calcium surplus are increase of the bone resorption marker CTX, suppressed PTH, in addition to an increase of urinary calcium/creatinine ratio.

At present, we do not consider secondary surgical resection of the tumour to be warranted. The surgery in this case had to be performed intralesionally due to the difficult tumour location with complete destruction and destabilization of the first sacral segment and compression of neural structures. The goals of the surgery were to decompress neural structures and to graft and stabilize the lumbopelvic junction, and these goals were met. The fibular allografts between L5 and S2 end plates and the morcellized bone grafts in the large lateral mass resection cavities all have healed well, stability of the lumbopelvic junction has been restored biologically, neural structures remain free, and the patient has no symptoms. The calcified tumour residues are located anteriorly to the promontory, where they do no mechanical harm. Because radical surgery in this case is beyond reach, we consider surgical reduction of these tumour residues to be of no value.

In case of regrowth of GCTB and unresponsiveness to intensified denosumab treatment, radiotherapy may be considered. Though effective in controlling disease progression and alleviating symptoms, radiotherapy can increase the risk of GCTB malignant transformation from a cumulative incidence of 1.6 % (spontaneous primary transformation) to 4.8 % (Palmerini et al., 2019). Radiotherapy should therefore only be considered in absence of any other treatment option.

4. Conclusion

Adjuvant treatment with zoledronate failed to control tumour growth, whereas denosumab treatment evaluated after 21 months controls tumour growth and relives pain, with asymptomatic side effects of hypocalcemia, hypophosphatemia and sclerosis of newly formed bone. As BSAP is readily available in many laboratories and cheap, we suggest BSAP to be a useful marker of tumour growth and activity. GCTB at all ages, that cannot be completely removed surgically, probably needs lifelong medical treatment to ensure tumour control, in this case denosumab was suggested to be the best treatment option. The expected consequences of *not* treating with denosumab in rare RANKL-mediated disorders in children must clearly outweigh the side effects on the total skeleton (as sclerosis and reduced bone remodelling) and the unknown long-term effects of denosumab treatment in children.

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CRediT authorship contribution statement

Signe Sparre Beck-Nielsen: Conceptualization, Writing – original draft, Writing – review & editing. **Henrik Hasle:** Conceptualization, Writing – review & editing. **Akmal Safwat:** Conceptualization, Writing – review & editing. **Kestutis Valancius:** Conceptualization, Writing – review & editing. **Bente Langdahl:** Conceptualization, Writing – review & editing. **Ebbe Stender Hansen:** Conceptualization, Writing – review & editing.

Declaration of competing interest

Signe Sparre Beck-Nielsen is a consultant for and has received research funding, honoraria, speakers fee and support for attending meetings from Kyowa Kirin. She participates in advisory boards, receiving honoraria from Kyowa Kirin and a data safety monitoring board, receiving honoraria from Inozymes.

Henrik Hasle has received a grant from XP4 for a clinical trial, a honorarium from Sanofi for a lecture, and is member of an advisory board funded by Novartis and chairs the international paediatric AML group (unpaid).

Akmal Safwat: there are none.

Kestutis Valancius: there are none.

Bente Langdahl received grants from Samsung Pharma and Mereo Pharma to institution for clinical trials, consulting fees from UCB pharma, payed lectures by Amgen, UCB, Eli Lilly, Gedeon-Richter, Astellas and Astra-Zenica, is participating in advisory boards for UCB Pharma and Gedeon-Richter and chairs the International Federation of Musculoskeletal Research Societies, unpaid.

Ebbe Stender Hansen: there are none

Data availability

Data will be made available on request.

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Written, informed consent for this case presentation was obtained from the parents.

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