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Case Report

Canakinumab in addition to phosphate-binding and phosphaturia-inducing therapy were effective in achieving remission in a child with a large familial calcinotic tumour

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ABSTRACT

We describe the clinical evolution of a patient with tumoral calcinosis due to a pathogenic variant in the *GALNT3* gene presented with a large mass overlying her left hip associated complicated by inflammatory flares. Therapy (sevelamer, acetazolamide, and probenecid) was unsuccessful in preventing tumour surgeries, therefore, interleukin-1β monoclonal antibody therapy was added; this was successful in the prevention of tumour re-growth. This case highlights the importance of assessing and treating the inflammatory aspect of calcinotic tumour.

1. Introduction

Hyperphosphatemic familial tumoral calcinosis (FTC) (OMIM# 211900) is a rare autosomal recessive disorder caused by pathogenic variants in the genes encoding one of the following proteins: fibroblast growth factor 23 (*FGF23*, 12p13.3) (Benet-Pagès et al., 2005), UDP-GalNAc: polypeptide *N*-acetylgalactosaminyl- transferase-T3 (*GALNT3*, 2q24–q31) (Topaz et al., 2004) or Klotho (*KL*, 13q12) (Ichikawa et al., 2007). The pathogenic variants result in a relative deficiency of, or resistance to, the phosphaturic hormone fibroblast growth factor 23 (FGF23).

Lack of FGF23 results in hyperphosphatemia due to increased renal tubular reabsorption of phosphate (TRP), and elevated or inappropriately normal 1, 25-dihydroxyvitamin D levels, both of which promote gastrointestinal absorption of phosphate and calcium. The net effect is an increase in the calcium × phosphate product, leading to ectopic calcifications that are most frequent in peri-articular locations such as the hips, elbows, and knees, but which can also occur elsewhere including large and small vessels. In addition to causing pain at the site of tumoral growth, the lesions are associated with local and systemic inflammatory reactions that can result in fever, malaise, and anemia of chronic disease. It has been suggested that these flares are related to interleukin-1 production by macrophages within the calcifications (Ramnitz et al., 2016).

A number of treatment approaches have been implemented with variable responses, including low phosphate diets, agents which decrease intestinal phosphate absorption (sevelamer, aluminum hydroxide), those which increase calcium-phosphate solubility by lowering serum pH (acetazolamide, a carbonic anhydrase inhibitor), phosphaturic therapies (such as probenecid and nicotinamide), those which "lock" phosphate in the skeleton (anti-resorptive agents), and topical anti-mineralization cream (thiosulfate). In patients with systemic inflammation, interleukin-1β antagonists have also been shown to significantly decrease inflammatory markers and reduce peri-lesional

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inflammation (Ramnitz et al., 2016; Boyce et al., 2020).

Here we describe the clinical trajectory of an 11-year-old girl with tumoral calcinosis due to homozygous pathogenic variants in *GALNT3* (c.1201T>C [p.Cys401Arg]) located in exon 6, who presented at 18 months of age with hyperphosphatemia and a large calcified mass overlying the left hip. Given the rarity of this condition, we describe our experience treating this patient, including her response to phosphate-binding therapy, intravenous zoledronic acid, topical anti-mineralization cream, phosphaturic treatment, and a carbonic anhydrase inhibitor (the latter, with the goal to increase calcium-phosphate solubility). We particularly highlight the inflammatory component of her condition and her response to interleukin-1β monoclonal antibody therapy. Permission was obtained to publish the case report according to local research ethics board requirements.

2. Case

2.1. Initial patient assessment

This 11-year-old girl was assessed by the pediatric orthopedic service at two years of age for an enlarging calcified mass overlying the left greater trochanter. The mass was first noted by parents at 18 months of age, and gradually increased in size. X-rays showed a 7.5 × 5.4 cm calcified mass lateral to the left hip, in adjacent soft tissue (Fig. 1). The lesion was de-bulked at three years of age, and the pathology was consistent with tumoral calcinosis. In addition, the biochemistry prior to the first surgery showed a high phosphate level for age at 2.74 mmol/L (N: 1.33–1.92), an elevated tubular reabsorption of phosphate (99.7 %), and a high tubular maximum reabsorption of phosphorus/glomerular filtration rate (TMPmax/GFR) at 2.69 mmol/L (N: 0.97–1.64); these results were consistent with an inability to excrete phosphate. In addition, the serum 1, 25-dihydroxyvitamin D level was inappropriately normal for the degree of hyperphosphatemia at 88 pmol/L (N: 39–193), parathyroid hormone (PTH) was normal at 2.5 pmol/L (N: 1.6–9.3) and serum ionized calcium was also normal at 1.31 mmol/L (N: 1.16–1.36). However, serum C-terminal FGF23 was predictably high at 1435 RU/ml (N < 230), given the lack of O-glycosylation arising from the pathogenic variant that normally retains the full-length, biologically active FGF23 molecule intact. Genetic testing identified a homozygous pathogenic variant in the *GALNT3* gene (c.1201T>C) [p.Cys401Arg], which corroborated the clinical presentation.

2.2. Therapeutic intervention of the tumoral calcinosis follow-up and outcomes

Following the initial debulking surgery, the lesion was reduced to 2.5 × 2.9 cm on plain x-ray. Immediately post-operatively, a low phosphate diet plus intestinal phosphate-binding with calcium carbonate were initiated. These modest measures were undertaken while awaiting special access to sevelamer and acetazolamide. At 3 years and 8 months of age, she transitioned to sevelamer (starting dose 50 mg/kg/day divided among meals and snacks) and acetazolamide (8 mg/kg/day divided twice daily, as shown in Fig. 2 (which shows her polypharmacy mapping throughout her clinical course)). The biochemical goal of acetazolamide was to achieve a venous pH between 7.2 and 7.35, bicarbonate 18–20 mmol/L, and base excess −3 to −5 mmol/L, which was successfully achieved on an average dose of acetazolamide 12 mg/kg/day over the ensuing 7 years.

Adherence to multiple doses of two medications per day in a young child was understandably challenging, rendering it difficult for the medical team to assess whether the tumour progression was due to a lack of medication adherence or refractoriness to therapy. A follow-up MRI performed 8 months after the surgery revealed a large tumour of 11.8 × 10.6 × 7.2 cm within the gluteus maximus muscle. This tumour size

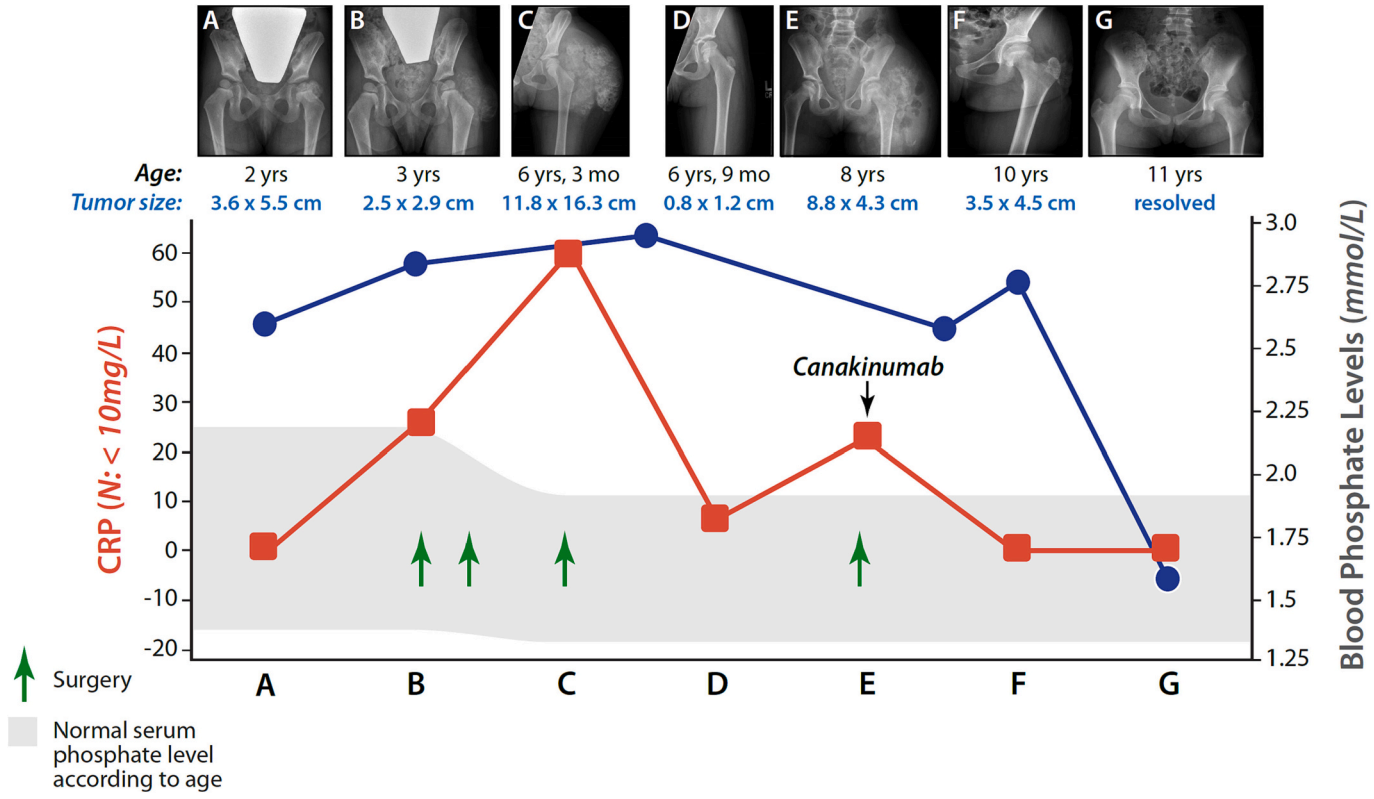

Fig. 1. This figure shows the left hip calcinotic tumour burden (in blue) from diagnosis (at 2 years of age) to the last follow-up (at 11 years 4 months of age) in relationship to c-reactive protein levels (in red). She was treated with sevelamer, acetazolamide and probenecid, to which canakinumab was added at 8 years and 2 months of age. Abbreviations: CRP = c-reactive protein; N = normal.

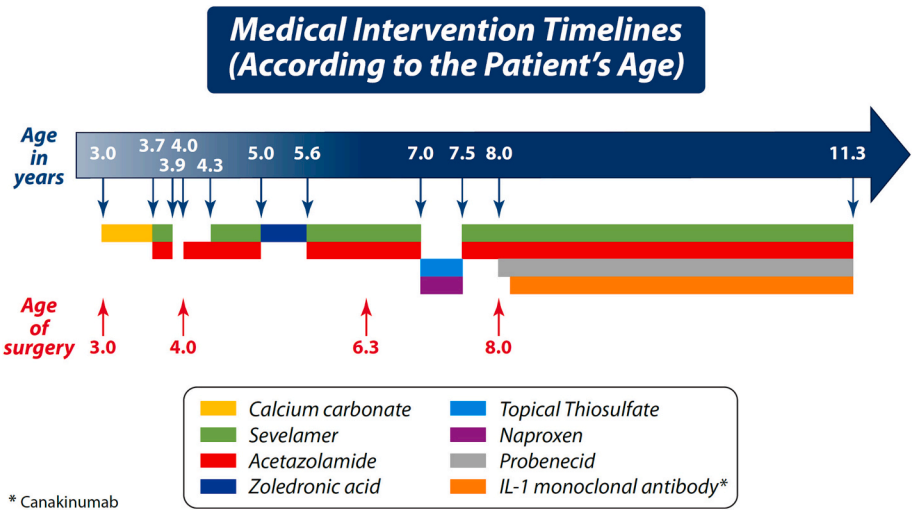

Fig. 2. This figure shows the timeline map for the patient'as polypharmacy to treat the aggressive left hip tumoral calcinosis, including: 1. Oral Acetazolamide: starting dose = 8 mg/kg/day in 2 divided doses; maximum dose = 15 mg/kg/day in 2 divided doses; 2. Oral Sevelamer: starting dose = 800 mg with meals, and 400 mg with snacks; maximum dose = 1600 mg with each of three meals and 800 mg with snacks, maximum of three snacks per day; 3. Intravenous zoledronic acid: starting dose 0.025 mg/kg followed by 0.025 mg/kg Q 3 months, for 3 doses; 4. Topical thiosulfate: 25 % thiosulfate applied to the area once per day at night; 5. Oral Naproxen: starting dose 10 mg/kg/day in 2 divided doses; maximum dose 14 mg/kg/day in 2 divided doses; 6. Oral probenecid: starting dose 18 mg/kg/day in 2 divided doses; maximum dose 20 mg/kg/day in 2 divided doses; 7. Sub-cutaneous canakinumab: starting dose 2.5 mg/kg every 8 weeks; maximum dose 2.5 mg/kg/day every 8 weeks.

reached a critical threshold that affected hip mobility and caused pain; therefore, she underwent a successful second tumour de-bulking surgery at four years of age.

Following the second de-bulking surgery, a lapse in access to sevelamer occurred such that she was only re-started on the therapy four months post-operatively (and therefore received acetazolamide monotherapy during this time). At five years of age, in the face of progressive tumour recurrence, she was tried on a course of intravenous zoledronic acid (0.025 mg/kg every 3 months, two infusions in total) for which there was precedent in the literature (Balachandran et al., 2014). Interestingly, the palpable calcinotic tumour softened on zoledronic acid but did not regress.

While on zoledronic acid for seven months, the tumoral growth velocity increased, and it was concluded that intravenous zoledronic acid should be discontinued. The mass once again reached a critical size, measuring approximately 11.8 × 16.3 × 13.2 cm on MRI. In addition, the patient was unwell with intermittent fever, fatigue, malaise, microcytic anemia, and high inflammatory markers. Despite reluctance to operate again, a third debulking surgery was necessarily performed (at 6 years 3 months of age) due to pain. Fig. 1 shows the relationship between serum c-reactive protein (CRP) levels and the size of the tumour on plain radiographs in the first six years of life, during which time she had three debulking surgeries. Due to the distinct opacification of the tumour allowing it to be readily visualized on plain X-rays, the fact that the calcinotic tumour was easily palpable over the left hip, plus the clear relationship between tumour size on plain X-rays and clinical indicators of disease progression (including CRP levels, the degree of anemia, and recurrent fevers), we did not seek repeated CT and MRI imaging to capture the evolution of the tumour in this case.

Immediately following the third debulking surgery, sevelamer and acetazolamide were restarted, initially with improved medical adherence. At 7 years of age, naproxen was added when the CRP rose to 22.4 mg/L ($N < 10$). Adherence to sevelamer and acetazolamide once again lapsed, so a trial of topical thiosulfate 25 % (applied once per day at night) was attempted to ease the burden of oral therapy. Despite naproxen and topical thiosulfate, at 7 years 6 months of age, an X-ray of the lesion once again showed a rapid and significant progression of the tumour. Therefore, the naproxen and topical thiosulfate were discontinued, and she was placed back on sevelamer and acetazolamide.

At 8 years of age, the tumour continued to grow, associated with pain and perforation of the skin due to calcinotic fluid leakage (which appeared as milky white fluid intermixed with blood); as such, she underwent her fourth de-bulking surgery. Her inflammatory parameters were correspondingly increased (serum CRP 45 mg/L [N: <10] and ESR 61 mm/h [N: <34]), associated with intermittent fevers, leukocytosis, thrombocytosis, and microcytic anemia. At this juncture, probenecid 20 mg/kg/day (250 mg twice daily) was added to the sevelamer and acetazolamide. However, the likelihood of recurrence was felt to be high due to ongoing issues with medication adherence combined with the significant inflammatory component; therefore, canakinumab 2 mg/kg every 8 weeks (IL-1 monoclonal antibody) was also added to the medication regimen, two months after the introduction of probenecid. With this four-therapy approach, there was an absence of tumour recurrence until there was a lapse in her adherence to sevelamer, resulting in calcinotic leakage from the surgical wound at 10 years and four months of age. It was decided that the best course of action was for her to undergo drainage of the calcinotic liquid and to re-emphasize the need for the sevelamer.

Following debridement, she remained on the same polypharmaceutical approach, including sevelamer 1600 mg with each of three meals per day and 800 mg with each of a maximum of three snacks per day. In addition, she continued on acetazolamide 250 mg twice daily (12 mg/kg/day), probenecid 500 mg am and 250 mg pm (18 mg/kg/day), and canakinumab 100 mg (2.5 mg/kg every 8 weeks). On this treatment, combined with improved overall adherence to oral therapy and 100 % adherence to hospital-administered canakinumab, there was no further growth of the lesion. At the last evaluation (11 years of age), the serum phosphate (1.66 mmol/L; N: 1.33–1.92) and inflammatory markers (both ESR and CRP) were normal. Fig. 1 shows the relationship between CRP levels and the appearance of her tumour on plain radiography up until the most recent clinical visit. During this time, she has not manifested tumoral calcinosis lesions at other sites, reports feeling well, and is thriving in her day-to-day activities.

3. Discussion

We report a child with HFTC due to a homozygous, loss of function pathogenic variant in *GALNT3* complicated by inflammatory flares, which is a previously described phenomenon in this disease (Ramnitz et al., 2016). The clinical spectrum of HFTC is variable, ranging from isolated eyelid calcifications to massive periarticular and vascular involvement. Our patient demonstrated the most common location for calcinotic lesions - the lateral aspect of the hip within the abductor muscles. The calcified tumours have the potential to become very large and cause severe limitations in joint movements, in addition to pain and extravasation of fluid through the overlying skin (as experienced in our patient). She also presented constitutional inflammatory symptoms (fever, fatigue, malaise, microcytic anemia, and raised inflammatory markers), all of which were testament to the systemic impact of the focal calcinotic tumour. The relationship between HFTC and inflammation is

proposed to be that hydroxyapatite crystals become engulfed by macrophages which secrete inflammatory cytokines that perpetuate the tumour progression (Ramnitz et al., 2016). Our patient's clinical course was further complicated by understandable challenges in achieving adherence to the polypharmacy of oral therapy as a preschooler and young child.

Since there is a lack of high-quality clinical trials in HFTC, the treatment options are mainly based on case reports and series (Boyce et al., 2020). Medical therapies chiefly focus on lowering serum phosphate levels and decreasing inflammatory markers, in addition to improving pain, mobility, and halting tumour progression. The response to medical therapy is variable among patients, some of which may be attributed to understandably poor adherence to the difficult dosing regimens as in our patient, which occurred particularly when she was a younger child.

Most affected patients are treated with multiple daily doses of sevelamer with meals and snacks, a phosphate-binding agent that decreases dietary intestinal phosphate absorption. Combinatorial approaches are also prescribed, including phosphaturia-inducing therapy such as acetazolamide (a carbonic anhydrase inhibitor) and probenecid (a uricosuric agent which promotes renal phosphate excretion). The acidosis of acetazolamide also increases the solubility of calcium and phosphate, which prevents their precipitation (Ichikawa et al., 2010; Lammoglia and Mericq, 2009; Favia et al., 2014; Leibrock et al., 2016); with this therapy, monitoring serum bicarbonate to avoid significant acidosis is important. In some cases, acetazolamide and phosphate binders are sufficient to bring about complete resolution of the calcinotic tumours (Yamaguchi et al., 1995; Finer et al., 2014); in others, this approach has been successful in decreasing the size, reducing the progression, and preventing the formation of new lesions in the absence of complete remission (Lammoglia and Mericq, 2009). Topical sodium thiosulphate (which increases the solubility and excretion of calcium through chelation, and acts as an antioxidant to reduce inflammation) has also been used effectively in some patients, and bisphosphonate therapy has also (rarely) been reported to decrease the size of calcific lesions (Boyce et al., 2020; Doneray et al., 2021). In our patient's case, these therapies were not successful in bringing about clinically meaningful improvements in her disease trajectory.

Patients with hyperostosis and inflammatory signs may respond to non-steroidal anti-inflammatory drugs (NSAIDs); however, in our patient's case, the disease was too aggressive to respond to prostaglandin inhibition. Some patients have responded to anti-interleukin-1 therapies, including anakinra (interleukin-1 receptor blocker) and canakinumab (IL-1 monoclonal antibody), with promising results (Ramnitz et al., 2016; Dauchez et al., 2019). In our patient, the rise and fall of inflammatory markers correlated with the size of the tumour. It has been hypothesized that chronic inflammation may contribute to the recruitment/development of local progenitor cells with the osteogenic potential to form ectopic bone, possibly similar to the mechanism of heterotopic ossification in fibrodysplasia ossificans progressiva (Dauchez et al., 2019). Our patient's clinical evolution did indeed suggest that inflammation played a role in the pathogenesis and propagation of her disease, given that the introduction of canakinumab appeared to play important role in reversing inflammation and preventing tumour recurrence. After 4 cycles of tumour re-growth to the point of needing surgery, four-therapy polypharmacy (including canakinumab) appeared to be successful in preventing tumour recurrence in a way that was not possible with modulation of phosphate homeostasis alone. Interestingly, even while on canakinumab, her tumour relapsed slightly when access to sevelamer was temporarily interrupted; this suggests that combinatorial therapy was indeed required in order to maintain overall remission. Importantly, the addition of probenecid at 8 years of age was also associated with the longest sustained period of remission that was experienced so far.

Together, these observations suggest that a multi-pronged therapeutic approach to this girl's HFTC was germane to her overall favourable clinical trajectory. This also suggests, unfortunately, that de-escalation of medical therapy in an effort to ease the burden of combinatorial therapy is not a viable option. Our patient's clinical trajectory further highlights that early, rather than late, introduction of interleukin-1β antibody therapy may be needed in patients with high inflammatory markers in order to prevent tumour progression and the need for de-bulking surgery.

It should also be recognized that this condition has large phenotypic variability, with case reports highlighting a variety of treatment approaches and therapeutic responses (Ramnitz et al., 2016; Boyce et al., 2020). As such, there is critical need for a deeper understanding of the longitudinal natural history of this condition, in addition to further development of effective therapies. In the meantime, clinicians must continue to comprehensively monitor their patients and implement a management plan that is appropriate for a given situation.

4. Conclusion

This report highlights that combinatorial therapy including agents that target phosphate homeostasis in addition to interleukin-1β monoclonal antibody therapy may be needed in pateints with HFTC who manifest significant pain, tumour burden, and signs of systemic inflammation. In our patient's case, the size of the tumour and its relationship to serum inflammatory markers, along with the favourable inflammatory marker response to interleukin-1β antibody therapy, suggested that inflammation played a significant role in the pathogenesis of her disorder. Overall, our experience in the management of this patient was that four-drug therapy targeting phosphate homeostasis plus aggressive treatment of the inflammatory component of her disease were important aspects of tumour recurrence prevention.

CRediT authorship contribution statement

Maria Ochoa: Data curation, Investigation, Writing – original draft, Visualization, Formal analysis, Software. **Roman Jurencak:** Data curation, Resources, Writing – review & editing. **Kevin Smit:** Project administration, Resources, Writing – review & editing. **Sasha Carsen:** Investigation, Resources, Writing – review & editing. **Sarah L. Sawyer:** Data curation, Investigation, Resources, Writing – review & editing. **Marie-Eve Robinson:** Data curation, Investigation, Writing – review & editing, Resources. **Karine Khatchadourian:** Data curation, Resources, Writing – review & editing. **Hooi Peng Cheng:** Data curation, Resources, Writing – review & editing. **Marika Pagé:** Project administration, Writing – review & editing. **Joel Werier:** Investigation, Resources, Writing – review & editing. **Leanne Marie Ward:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

LMW has participated in clinical trials with ReveraGen, Ascendis, PTC, Catabasis, Novartis, Ultragenyx and Amgen, received unrestricted educational grants from Alexion, Ipsen and Ultragenyx, and received consulting fees from Santhera, Ipsen, Ultragenyx, PTC, Novartis, and Amgen (with funds to LMW's institution). MER has participated in clinical trials with Amgen. SC has received research grant funding from Zimmer Biomet and ConMed Linvatec, consulting fees for assisting with surgical training from Stryker and Smith & Nephew, and has participated in a clinical trial with Ascendis Biopharma (with funds to SC's institution). KS has consulted for Medtronic and has received research grants from Meditronics, Ascendis and SpinoModulation (All funds to Dr. Smit's institution). The other co-authors have no competing interests to declare.

Data availability

Data will be made available on request.

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MER is supported by a Junior Clinical Research Chair in Genetic Skeletal Disorders from the University of Ottawa and the Children's Hospital of Eastern Ontario Research Institute.

Ethical approval and informed consent

Written consent was obtained from the patient and/or caregivers in line with the Children's Hospital of Eastern Ontario Research Institute Ethics Board requirements.

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