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Case Report

Treatment With Romosozumab In Progressive Pseudorheumatoid Dysplasia

Nicolò Bisceglia,[1,2] Emanuela Scarano,[3] Anna Piazza,[1,2] Alessandra Gambineri,[1,2] Uberto Pagotto,[1,2] and Guido Zavatta[1,2]

[1]Division of Endocrinology and Diabetes Prevention and Care, IRCCS Azienda Ospedaliero-Universitaria, Bologna 40138, Italy
[2]Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum University of Bologna, Bologna 40138, Italy
[3]Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna 40138, Italy

Correspondence: Guido Zavatta, MD, PhD, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Via Giuseppe Massarenti, 9, Bologna, Emilia-Romagna 40138, Italy. Email: guido.zavatta@unibo.it.

Abstract

Progressive pseudorheumatoid dysplasia (PPD) is a rare genetic disorder caused by pathogenic variants in Wnt1-inducible signaling pathway protein 3 gene. The primary skeletal issues include progressive joint stiffness, bone deformities, and bone fragility. Patients with PPD may have a higher risk of fractures resulting from secondary osteoporosis, joint instability, and skeletal weakness. Because PPD is a rare condition with limited specific treatment guidelines, antifracture therapies that are commonly used for osteoporosis and other bone dysplasias may be considered, although these have never been tested in PPD itself. In this context, romosozumab, a monoclonal antibody primarily used in the treatment of postmenopausal osteoporosis, could represent a valid option for initiating a sequential antifracture therapy in patients affected by PDD with very low bone mineral density aiming to potentially reduce fracture risk as described in the present case report.

Key Words: progressive pseudorheumatoid dysplasia, *WISP3* gene, romosozumab, zoledronate, severe osteoporosis, antifracture treatment, sequential therapy

Introduction

Progressive pseudorheumatoid dysplasia (PPD; OMIM #208230) is a rare, autosomal recessive, disorder of postnatal skeletal and cartilage development first described in 1982 [1]. It has been estimated to occur in approximately 1/1 000 000 people in the United Kingdom, but it is likely to be higher in Turkey, India, and in the Middle East and Gulf States [2]. PPD is caused by pathogenic variants in Wnt1-inducible signaling pathway protein 3 *(WISP3)* gene, a growth factor that plays a major role in maintaining cartilage integrity by regulating the expression of type II collagen and aggrecan in chondrocytes. Therefore, *WISP3* gene is essential for bone formation and cartilage development [3] and the Wnt signaling pathway is known to influence bone mineral density (BMD) [4]. More than 70 *WISP3* pathogenic variants have been identified, but no genotype-phenotype correlation has been reported [5]. PPD typically onsets between the ages of 3 and 8 years and it is characterized by polyarticular involvement with interphalangeal joint swelling and pain, gait abnormalities, and fatigability, and for these reasons, it can be misdiagnosed as juvenile idiopathic arthritis (JIA) or other pediatric musculoskeletal disorders. Negative inflammatory markers associated with a poor response to immunosuppressive therapy, negative serum rheumatoid factor, and the marked decrease in growth rate can help in the correct diagnostic pathway [6]. Other signs and symptoms that develop over time include permanently bent fingers (camptodactyly), enlarged finger and knee joints, and hip pain, which is a common problem in adolescence [7]. Regarding radiological features, metaphyseal enlargement of the interphalangeal joints is an early radiological finding; furthermore, affected individuals typically have flattened vertebral bodies in the spine (platyspondyly) and bullet-like vertebral changes, leading to an abnormal front-to-back curvature of the spine [8]. Skeletal changes progress with age and are responsible for short adult stature, kyphoscoliosis, joint contractures, prolonged immobilization, and secondary osteoporosis [7]. For these reasons, patients affected by PDD have an increased fracture risk, but currently there is no definitive cure for PPD, and treatment mainly focuses on symptom management and improving the quality of life.

PPD is a rare disease and the available literature mainly includes single-case reports and only a few case series, so a gold standard for antifracture therapy has not yet been hypothesized. Therefore, this case is important because not only is it the first case reported in the literature in which romosozumab therapy was used successfully, but it could also be a hypothetical starting point on how to set up a sequential osteoporosis therapy to improve BMD in these patients.

Case Presentation

A 54-year-old Caucasian woman was referred to our outpatient clinic for bone mineral metabolism disorders with a diagnosis of PPD for a reassessment of antifracture therapy.

The patient was born at term to nonconsanguineous parents, a negative family history for musculoskeletal diseases,

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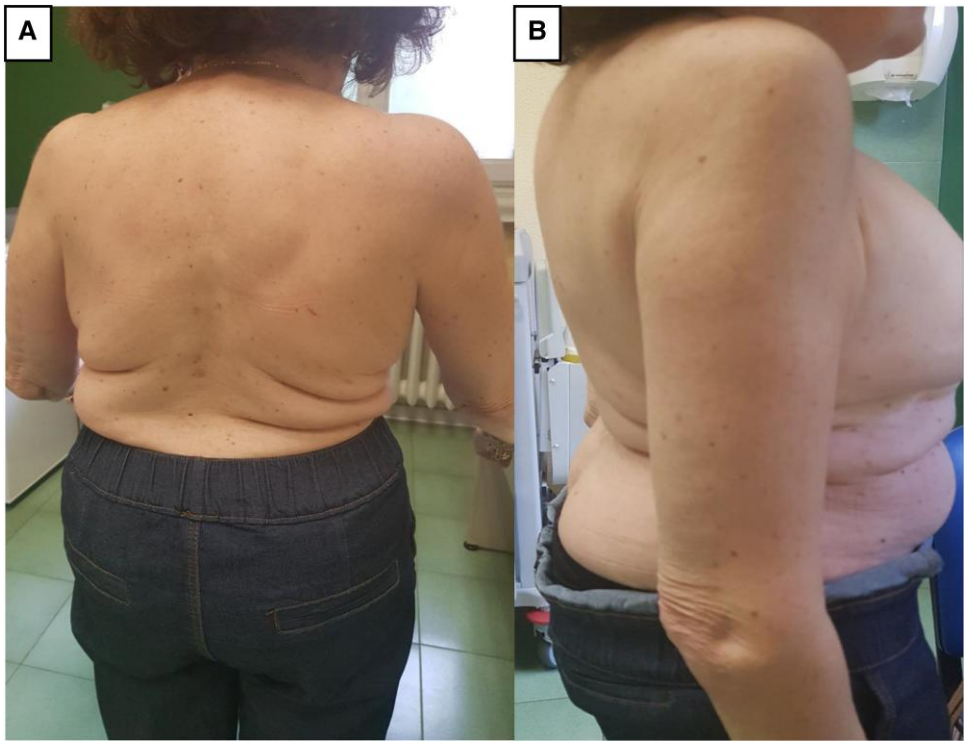


Figure 1. Patient had short adult size with a short trunk (A) and kyphoscoliosis (A and B).

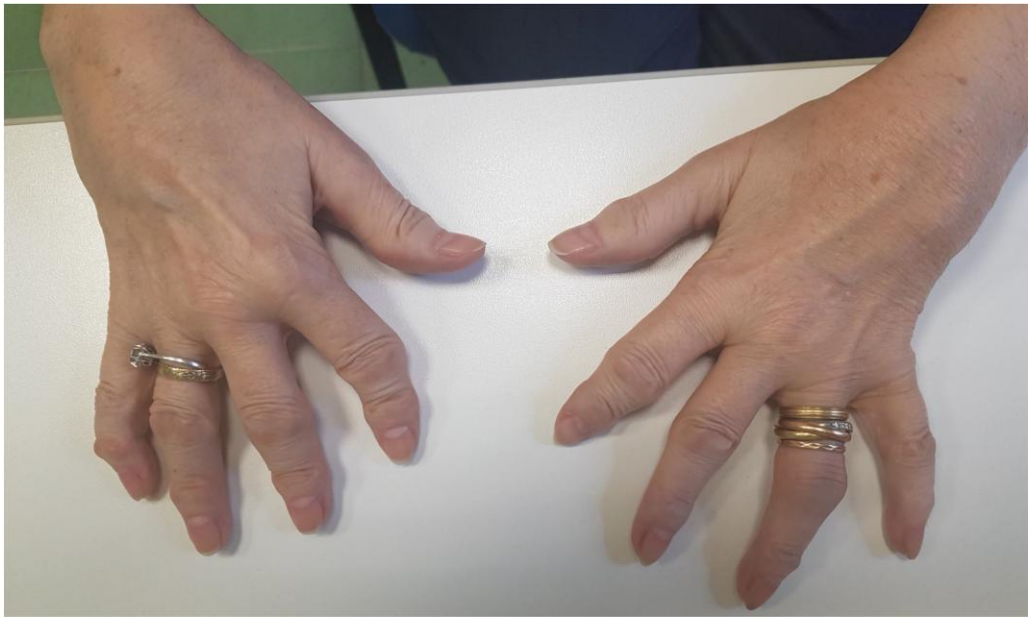


Figure 2. Enlargement of interphalangeal joints with permanently bent fingers (camptodactyly).

and no other significant pathologies in remote medical history. She had a regular menstrual cycle until spontaneous menopause at the age of 43 years, without hormone replacement therapy and no pregnancies or gynecological disorders. She underwent prolonged corticosteroid therapy with betamethasone for at least 10 years (from approximately age 12 to 32 years) in suspicion of JIA with even long periods of bed immobilization because of her disease. The diagnosis of low bone mass was made at age 37 years, when she performed her first lumbar spine (LS) dual-energy X-ray absorptiometry (DXA): L1-L4 BMD 0.565 g/cm^2; T-score −4.3; Z-score −4.0.

Regarding her clinical picture, the patient had short adult size with a short trunk and kyphoscoliosis (Fig. 1); in particular, her height was 140 cm, lower extremities were 67.5 cm, and trunk was 40 cm.

Other clinical characteristics were enlarged finger and knee joints, in particular enlargement of interphalangeal joints with camptodactyly (Fig. 2).

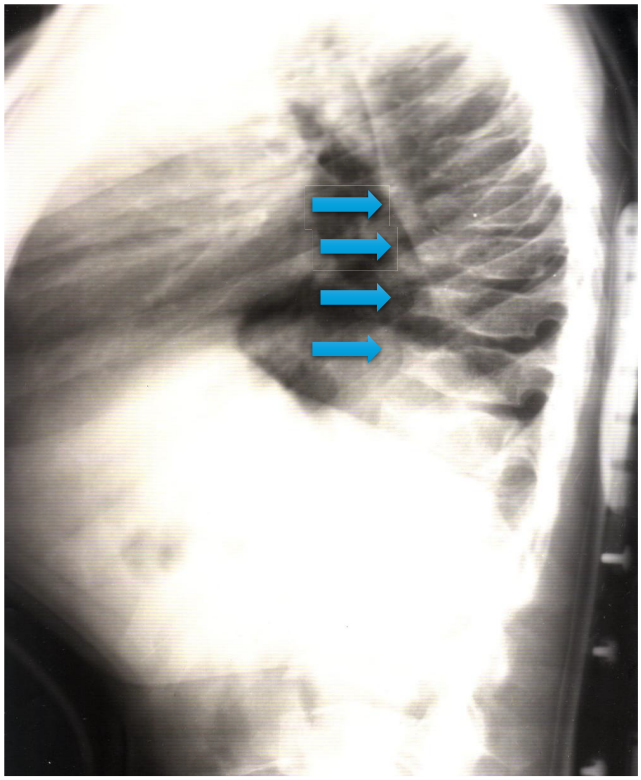


Figure 3. Lateral projection x-ray of the spine. Arrows highlight flattened vertebral bodies in the spine (platyspondyly) with typical bullet-shaped changes in several vertebrae.

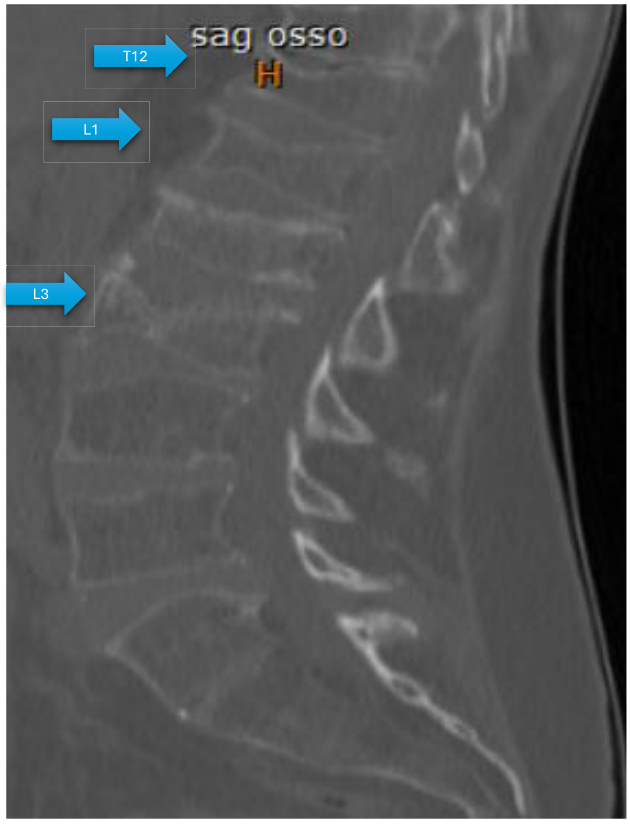


Figure 4. Computed tomography scan of the lumbar spine. The arrows highlight morphometric vertebral fractures of T12, L1, and L3 in the absence of apparent trauma.

Furthermore, the patient underwent multiple orthopedic surgeries because of bone deformities. She received a right femoral osteotomy at the age of 11 years, followed by a right hip prosthesis at age 27 years, which was subsequently revised. A left hip prosthesis was implanted at age 30 years, and a bilateral knee replacement was performed at age 44 years. At age 48 years, she sustained a humeral fracture from a fall at standing height; this was treated with internal fixation devices.

Diagnostic Assessment

She was admitted for the first time at age 6 years for polyarticular pain of uncertain interpretation that led to the initial diagnosis of mucopolysaccharidosis. Regarding her spine, a radiological picture of dysplastic alterations of vertebrae with flat morphology was reported (Fig. 3).

In a subsequent hospitalization at age 11 years, the diagnosis was reformulated to JIA, with predominant involvement of the joints of the hands and hips. The clinical picture progressively worsened at the hip level, to the point of preventing her from walking; she underwent a right osteotomy with notable functional benefit. However, during childhood, she faced periods of prolonged immobilization and was treated for years with betamethasone, indomethacin, and gold salts without significant clinical benefit.

At age 32 years, due to the worsening of symptoms and negativity of inflammation indices, a diagnosis of PPD was made. Subsequently, genetic testing confirmed the pathogenic variants in the *WISP3* gene, highlighting a composite heterozygosity (c.156C > A/c.236-237CC > AA).

Treatment

Regarding antifracture therapy, the patient attempted various treatments: at age 37 years, she started a treatment with oral risedronate 35 mg once weekly for 5 years without any clinical or radiological benefit; at age 44 years, she began a therapy with oral alendronate 70 mg once weekly. This was interrupted after a few months because of post-administration headaches; 3 years later, she started another antiresorptive therapy with subcutaneous injections of denosumab 60 mg/mL. This was also interrupted after only 1 administration because of diffuse myalgia.

She was referred to our adult endocrinology clinic at age 54 years and, considering her clinical and radiological picture, after an adequate supplementation with cholecalciferol 2000 IU daily, we proposed an osteoanabolic therapy with subcutaneous injections of teriparatide 20 mcg daily. The patient continued this therapy for approximately 12 months but it was subsequently interrupted because of persistent swelling and redness of the hands, which regressed after stopping teriparatide and switching to oral Ibandronate 150 mg once per month.

At age 57 years, she was admitted for acute low back pain during ibandronate therapy, and a computed tomography scan of the lumbar spine revealed vertebral fractures of T12, L1, and L3 in the absence of apparent trauma (Fig. 4).

After ensuring adequate calcium intake with calcium citrate 500 mg daily and cholecalciferol supplementation with 2500 IU daily, we set up sequential therapy starting from subcutaneous injections of romosozumab 210 mg monthly for

Table 1. Bone turnover markers before and after sequential therapy

Marker	Reference range	Day 0	Day 15	Month 1	Month 3	Month 6	Month 9	Month 12	6 months after zoledronate
BAP	**5.5-27.1 µg/L (5.5-27.1 U/L)**	46.5 µg/L (46.5 U/L)	111.0 µg/L (111.0 U/L)	120.2 µg/L (120.2 U/L)	61.8 µg/L (61.8 U/L)	43.0 µg/L (43.0 U/L)	33.7 µg/L (33.7 U/L)	27.7 µg/L (27.7 U/L)	16.1 µg/L (16.1 U/L)
P1NP	**27.7-127.6 ng/mL (27.7-127.6 µg/L)**	130.3 ng/mL (130.3 µg/L)	>230.0 ng/mL (>230.0 µg/L)	>230.0 ng/mL (>230.0 µg/L)	171.2 ng/mL (171.2 µg/L)	150.8 ng/mL (150.8 µg/L)	120.4 ng/mL (120.4 µg/L)	68.3 ng/mL (68.3 µg/L)	32.4 ng/mL (32.4 µg/L)
CTX	**0.142-1.351 ng/mL (0.142-1.351 µg/L)**	0.707 ng/mL (0.707 µg/L)	0.321 ng/mL (0.321 µg/L)	0.722 ng/mL (0.722 µg/L)	1.400 ng/mL (1.400 µg/L)	0.581 ng/mL (0.581 µg/L)	0.199 ng/mL (0.199 µg/L)	0.225 ng/mL (0.225 µg/L)	0.148 ng/mL (0.148 µg/L)

Bone turnover markers before the first administration of romosozumab, 15 days after the first administration, during months 1, 3, 6, and 9 of therapy, and at the end. We also performed bone turnover markers 6 months after zoledronate 5 mg infusion.
Specifications: Reference range is shown in bold font. Values in parentheses are International Système of Units (SI).
Abbreviations: BAP, bone alkaline phosphatase; CTX, C-terminal telopeptide of collagen type 1; P1NP, type 1 procollagen amino terminal peptides.

12 months with close clinical and biochemical monitoring, followed by antiresorptive therapy with intravenous zoledronate 5 mg.

The patient also underwent regular physiotherapy and oral tapentadol 100 mg once daily for pain management during the treatment period.

Outcome and Follow-up

Bone turnover markers (Table 1) were assessed at multiple time points during romosozumab treatment and again 6 months after zoledronate infusion, using a chemiluminescent immunoassay method according to standard laboratory procedures.

After 15 days of therapy, bone formation markers had more than tripled, whereas bone resorption markers were halved. At 1 month, bone resorption markers also increased and continued to rise until the third month, with formation markers remaining elevated. A subsequent overall decline in bone turnover was then observed during the second half of the treatment period. Six months after zoledronate infusion, bone turnover was globally reduced compared to baseline.

Regarding the densitometric profile, LS DXA performed 1 year before starting romosozumab showed osteoporosis (L1-L4 BMD 0.622 g/cm^2; T-score −4.7; *Z*-score −3.1). At the end of the 12-month treatment, BMD had increased by 24.0% (L1-L4 BMD 0.771 g/cm^2; T-score −3.4; *Z*-score −1.7) (Fig. 5). In contrast, distal radius BMD remained essentially unchanged throughout the same period (Fig. 6). DXA scans were performed using the same GE Lunar iDXA system in standard mode.

The patient reported good tolerance and excellent compliance with the therapy, with no reported significant side effects. She also reported clinical benefits after romosozumab therapy during physiotherapy sessions, especially in spinal mobility.

Discussion

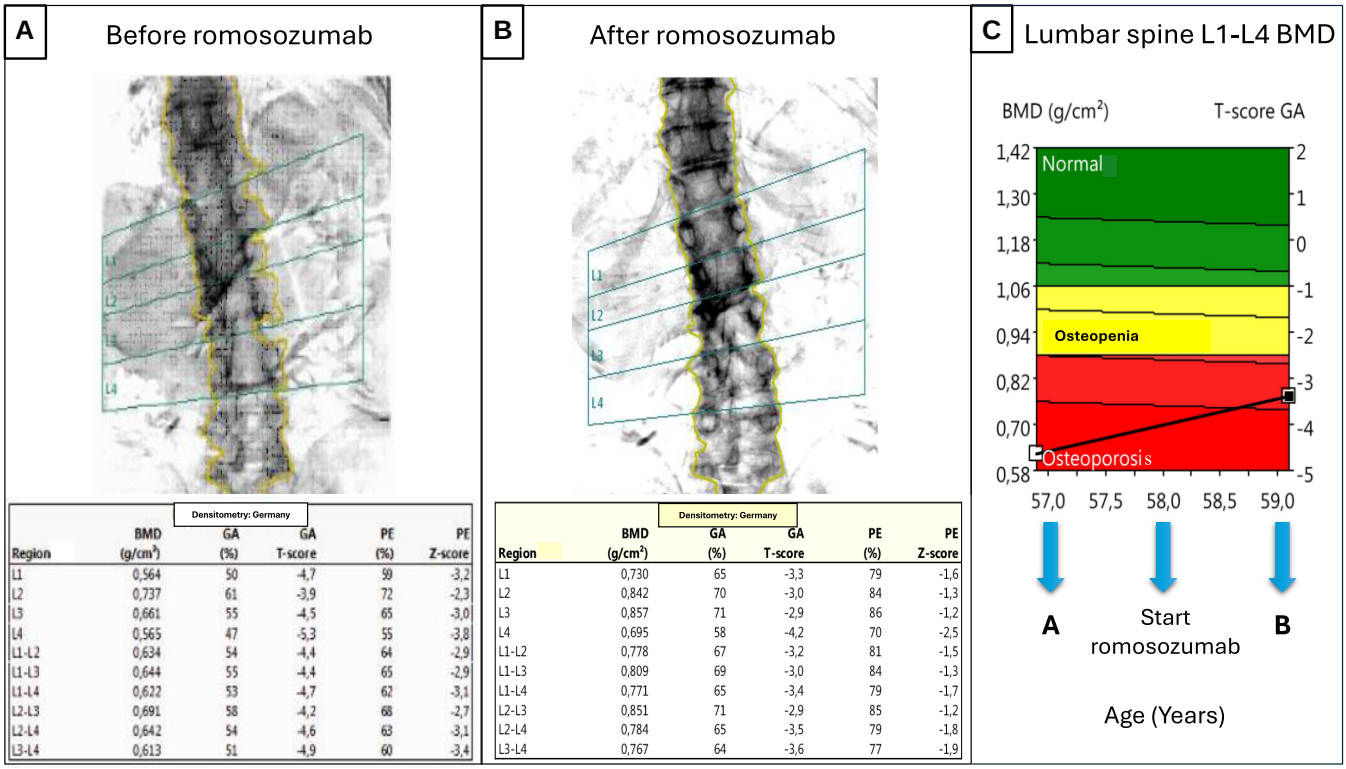
Antifracture therapy plays a crucial role in PDD treatment, as bone abnormalities and skeletal fragility can predispose individuals to fractures reducing expectancy and quality of life.

Additionally, some patients may be referred to a pediatric endocrinologist because of their short stature, so it is important to recognize this condition to avoid misdiagnosis and a prolonged period of unnecessary corticosteroid therapy that could worsen the bone condition.

Developing a tailored antifracture treatment strategy may represent an emerging area of interest; however, current scientific literature specifically addressing this condition is scarce, and no clinical practice guidelines are available. Moreover, the use of osteoporosis medications in PPD has been reported only rarely (Table 2).

In this regard, all patients reported in the literature [2, 9-12] received oral or intravenous antiresorptive treatment. In 1 case series [9] of 3 siblings treated with intravenous pamidronate, no significant BMD improvement was reported. In other cases [2, 10-12], the treatment response to bisphosphonates is not clearly documented, and data regarding tolerability or adverse effects are lacking. To our knowledge, no other antifracture treatments have been described in the literature.

This case highlights the potential of romosozumab as a part of sequential antifracture therapy in PPD. In our patient, the dual-acting effect of romosozumab was very clear especially



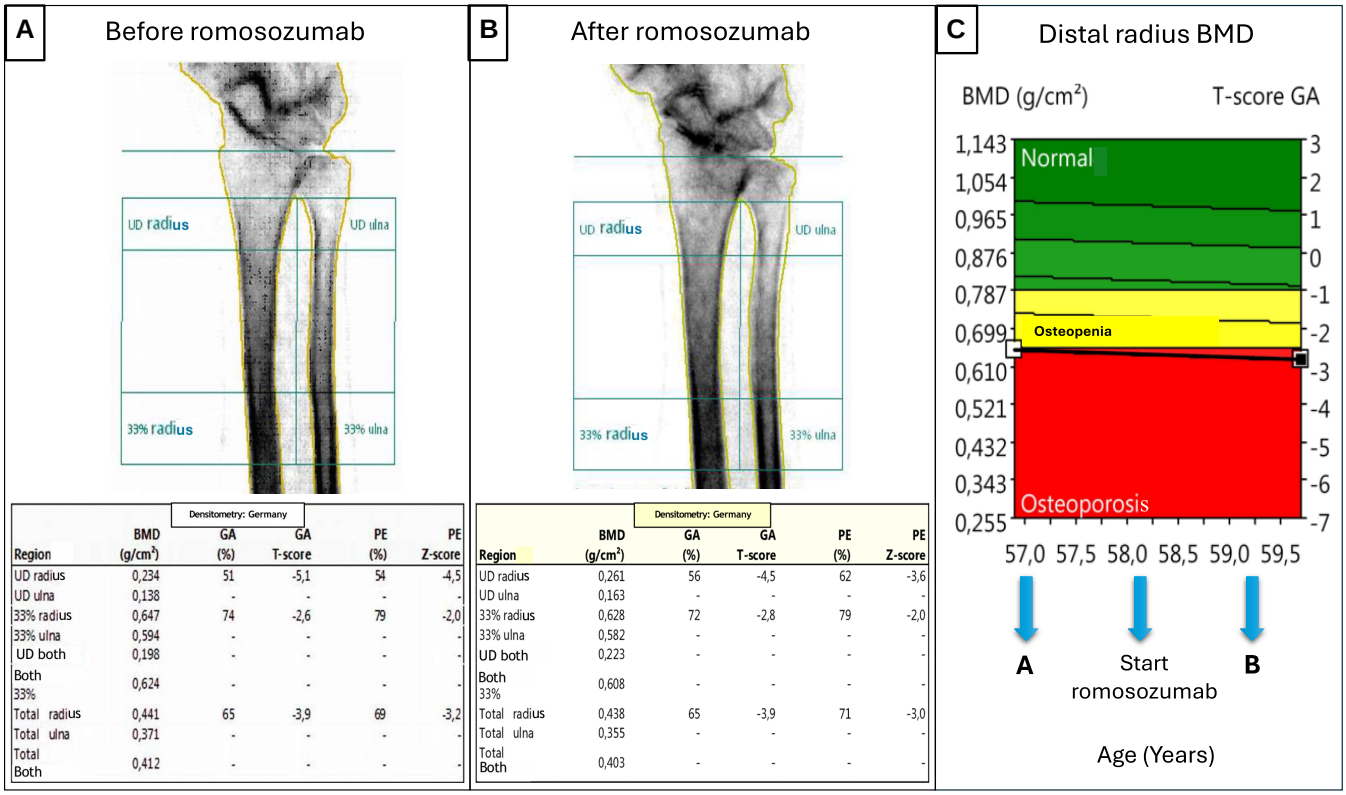
Densitometry: Germany

Region	BMD (g/cm²)	GA (%)	GA T-score	PE (%)	PE Z-score
L1	0,564	50	-4,7	59	-3,2
L2	0,737	61	-3,9	72	-2,3
L3	0,661	55	-4,5	65	-3,0
L4	0,565	47	-5,3	55	-3,8
L1-L2	0,634	54	-4,4	64	-2,9
L1-L3	0,644	55	-4,4	65	-2,9
L1-L4	0,622	53	-4,7	62	-3,1
L2-L3	0,691	58	-4,2	68	-2,7
L2-L4	0,642	54	-4,6	63	-3,1
L3-L4	0,613	51	-4,9	60	-3,4

Densitometry: Germany

Region	BMD (g/cm²)	GA (%)	GA T-score	PE (%)	PE Z-score
L1	0,730	65	-3,3	79	-1,6
L2	0,842	70	-3,0	84	-1,3
L3	0,857	71	-2,9	86	-1,2
L4	0,695	58	-4,2	70	-2,5
L1-L2	0,778	67	-3,2	81	-1,5
L1-L3	0,809	69	-3,0	84	-1,3
L1-L4	0,771	65	-3,4	79	-1,7
L2-L3	0,851	71	-2,9	85	-1,2
L2-L4	0,784	65	-3,5	79	-1,8
L3-L4	0,767	64	-3,6	77	-1,9

Figure 5. Lumbar spine dual-energy x-ray absorptiometry 1 year before starting romosozumab therapy, at age 57 years (A), and at the end of the 12-month treatment, at age 59 years (B). The percentage increase in BMD at L1-L4 was 24.0% (C).
Abbreviations: BMD, bone mineral density; GA, geometric area; PE, age percentage.



Densitometry: Germany

Region	BMD (g/cm²)	GA (%)	GA T-score	PE (%)	PE Z-score
UD radius	0,234	51	-5,1	54	-4,5
UD ulna	0,138	-	-	-	-
33% radius	0,647	74	-2,6	79	-2,0
33% ulna	0,594	-	-	-	-
UD both	0,198	-	-	-	-
Both 33%	0,624	-	-	-	-
Total radius	0,441	65	-3,9	69	-3,2
Total ulna	0,371	-	-	-	-
Total Both	0,412	-	-	-	-

Densitometry: Germany

Region	BMD (g/cm²)	GA (%)	GA T-score	PE (%)	PE Z-score
UD radius	0,261	56	-4,5	62	-3,6
UD ulna	0,163	-	-	-	-
33% radius	0,628	72	-2,8	79	-2,0
33% ulna	0,582	-	-	-	-
UD both	0,223	-	-	-	-
Both 33%	0,608	-	-	-	-
Total radius	0,438	65	-3,9	71	-3,0
Total ulna	0,355	-	-	-	-
Total Both	0,403	-	-	-	-

Figure 6. Distal radius dual-energy x-ray absorptiometry 1 year before starting romosozumab therapy, at age 57 years (A), and at the end of the 12-month treatment, at age 59 years (B). The percentage variation in BMD was −2.9% (not significant) (C).
Abbreviations: BMD, bone mineral density; GA, geometric area; PE, age percentage.

Table 2. Published cases of patients with PDD treated with antifracture drugs

First author and year	Study type	Age (years) and gender	Medication and dose	Densitometric parameters pre-therapy
Temiz et al (2011) [9]	Case series	15, female	Intravenous pamidronate, 1 mg/kg/day for 3 days every 3 months	LS *Z*-score −3.0; FN *Z*-score −4.4
Temiz et al (2011) [9]	Case series	14, male	Intravenous pamidronate, 1 mg/kg/day for 3 days every 3 months	LS *Z*-score −4.2; FN *Z*-score −4.6
Temiz et al (2011) [9]	Case series	3, male	Intravenous pamidronate, 1 mg/kg/day for 3 days every 3 months	LS *Z*-score −0.6; FN *Z*-score −0.9
Yurdakul (2015) [10]	Case report	21, male	Antiresorptive treatment, ND	LS L2-L4 BMD 0.759 g/cm^2; LS L2-L4 T-score −3.0; TH BMD 0.718 g/cm^2; TH T-score −2.4
Aytekin et al (2018) [11]	Case report	33, male	Alendronate, 70 mg/week	Left FN T-score −2.5; FN *Z*-score −2.2; LS L2-L4 T-score −3.0; LS L2-L4 *Z*-score −3.0
Giray et al (2019) [2]	Case report	23, female	Bisphosphonate, ND	LS *Z*-score −3.0
Chen et al (2022) [12]	Case report	31, male	Bisphosphonate, ND	Minimum *Z*-score −3.8 (not known if LS, TH, or FN)

Abbreviations: BMD, bone mineral density; FN, femoral neck, LS, lumbar spine; ND, no data; TH, total hip.

in the first weeks of therapy, but then the anabolic window was less evident, probably because of the previous antifracture therapy or maybe the intrinsic response in PDD itself. To our knowledge, this is the first bone marker profile in which the effect of romosozumab in PDD was documented, so we did not have a comparison to try to establish whether this might be an atypical response, compared to the response in other postmenopausal women.

Although no definitive conclusions regarding antifracture efficacy can be drawn from a single case and a short observation period, it is worth noting that our patient showed a favorable response in terms of BMD improvement, and no new fragility fractures occurred.

Furthermore, based on what the patient reported, we also assume a beneficial effect of romosozumab directly on the symptoms of PDD, in particular on pain and reduced mobility of the spine. However, better understanding its mechanism and how it may interact with this pathology can provide some other insights.

Learning Points

- PDD may be a rare cause of short stature in childhood, therefore it is important for a pediatric endocrinologist to recognize this suggestive picture to prevent prolonged and unnecessary corticosteroid therapy.
- In older patients with PDD, secondary osteoporosis and fragility fractures could become priority problems; therefore, setting up an effective antifracture therapy is essential, together with adequate supplementation with calcium and cholecalciferol and rehabilitation physiotherapy treatments.
- Despite the absence of specific indications on the management of antifracture therapy in PDD, a sequential therapy with romosozumab followed by zoledronate may be considered, particularly in patients with inadequate BMD response or incident fractures during antiresorptive treatment.
- Romosozumab appeared to provide some benefit for osteoarticular symptoms in PDD. However, further studies will be needed to confirm this.

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None.

Contributors

E.S. was involved in the diagnosis of the patient and N.B, G.Z., A.G., A.P., and U.P. were involved in the management of the patient. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from patient.

Data Availability Statement

All datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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