Journal of Clinical Densitometry: Assessment of Skeletal Health, vol. 15, no. 1, 116–119, 2012

1094-6950/15:116–119/$36.00
DOI: 10.1016/j.jocd.2011.10.001

Case Report

Complicated Osteoporosis in Progeroid Syndrome: Treatment With Teriparatide

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Abstract

Human progeroid syndromes (PSs) include a group of genetic ''premature aging'' diseases that affect a variety of organ systems. Bone diseases are common sequelae of patients diagnosed with PSs.

Teriparatide therapy is recommended for elderly men with low bone mineral density (BMD; T-score < -2.5) and at least 1 fragility fracture who are unable to tolerate bisphosphonates. We describe a 20-yr-old patient affected by PS and severe osteoporosis complicated with femoral fracture. The patient experienced a significant improvement in lumbar spine BMD after treatment with teriparatide.

Key Words: Fracture; osteoporosis; progeroid syndrome; teriparatide.

Introduction

Progeroid syndromes (PSs) are genetic disorders in which individuals exhibit certain features of aging early in life *(1)*. The phenotypic expression of PSs is highly variable and involves alterations of the skin, bone, and cardiovascular tissues. Bone disease is a determining factor in their quality of life, which is markedly deteriorated by osteoporosis and secondary pathologic fractures *(2)*. Therefore, aggressive treatment of osteoporosis must be warranted in patients with PS.

However, there is lack of information about management of osteoporosis in patients suffering from PS. Pharmacologic therapy of osteoporosis in elderly population includes oral bisphosphonates as first-line therapy. Because of its cost, subcutaneous route of administration, and long-term safety concerns, parathormone therapy is generally restricted to patients with severe osteoporosis (T-score: −3.5) or moderate osteoporosis (T-score: −2.5) plus history of fragility fracture.

We describe a 20-yr-old male with severe osteoporosis associated with PS after treatment with teriparatide.

Received 04/15/11; Revised 10/01/11; Accepted 10/02/11.

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Case Report

The patient was referred for consultation to treat his osteoporosis. Weight and height were normal for the patient at birth, but at the age of 12 mo, both his weight and height were below the third centile. At 2 yr of age, abnormalities of distal phalanges and decreased joint mobility were found, and he was initially diagnosed with mandibuloacral dysplasia PS. Pituitary assessment revealed growth hormone deficiency, and he was treated with growth hormone from age 3 to 15 yr. Growth hormone was stopped at the age of 15 yr when growth hormone response to insulin-induced hypoglycemia was documented to be normal.

Physical examination features showed alopecia, atrophic skin, beaked nose, micrognathia, lipodystrophy, distal phalangeal osteolysis, and dystrophic nails (Fig. 1A and B).

The patient's serum phosphorus level was 5.04 mg/dL (normal range: 2.5–4.5 mg/dL), bone alkaline phosphatase was 11.19 μg/L (normal range: 4–20 μg/L), and platelet counts were at 560.000 (normal range: 130.000–400.000). Genetic analysis revealed lack of mutations in lamin A/C (*LMNA*) and *ZMPSTE24* genes but identified a homozygous mutation in barrier-to-autointegration factor 1 (BANF1) *(3)*, a genetic mutation recently identified as the cause of a hereditary PS.

Bone mineral density (BMD) Z-scores of the patient were low, with lumbar spine Z-score of −6.2 and femoral neck

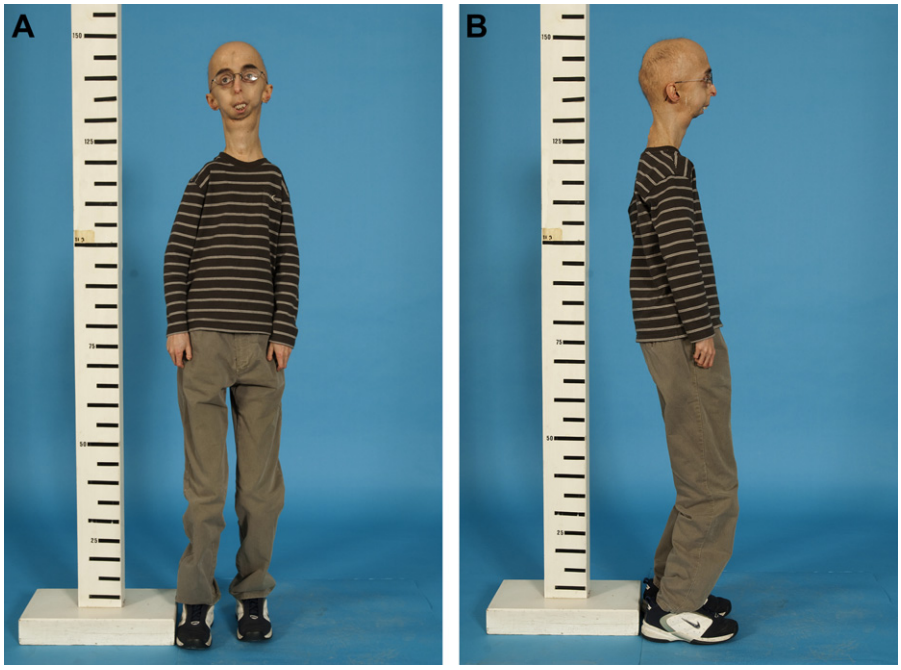

Fig. 1. (**A** and **B**) Patient at the age of 20 yr.

Z-score of −4.3. After causes of secondary osteoporosis were ruled out, calcium, vitamin D supplements, and weekly alendronate were started, but treatment was stopped after 8 mo because of diarrhea. Six months later, the patient suffered a pathologic subcapital femoral fracture and was started on teriparatide 20 µg subcutaneous, daily for 18 mo. Teriparatide was well tolerated despite mild hypercalcemia. Laboratory tests were performed at 0, 1, 3, 12, and 20 mo after initiation of treatment. BMD was assessed at 0, 18, and 36 mo after initiation of teriparatide (Hologic model QDR-4500W densitometer; Hologic Inc., Bedford, MA).

Basal serum calcium was 9.9 mg/dL (normal range: 8.5−10.5 mg/dL). Asymptomatic hypercalcemia (10.7 mg/dL) was observed within the first month after initiation of teriparatide, but it did not require changes in treatment. Ionized calcium and calciuria were normal during the treatment (Table 1). Serum total calcium reverted to normal levels 3 mo after discontinuation of teriparatide. No other laboratory or clinical adverse effect (as nausea or headache) was observed.

In the patient, lumbar spine BMD increased by 19.9% and Z-score increased from −6.2 to −5.4 after 18 mo, whereas hip BMD and Z-score remained stable (Table 2).

Discussion

PSs are rare inherited disorders caused by mutations in gene-encoding proteins involved in lamin A processing. The common molecular feature of progeroid laminopathies is the accumulation of prelamin A *(4)*. Progeroid laminopathies (including Hutchinson-Gilford, mandibuloacral dysplasia, atypical Werner syndrome, and restrictive dermopathy) are characterized clinically by premature aging and bone diseases, such as osteolysis and osteopenia *(2)*. Patients with the PS caused by BANF1 mutation present phenotypic overlapping between patients with Hutchinson-Gilford progeria syndrome and mandibuloacral dysplasia and suffer profound skeletal abnormalities; therefore, osseous manifestations are a priority in these patients. Although bony structures usually appear normal in early childhood, clavicular resorption, coxa valga, avascular necrosis of the femoral head, modeling abnormalities of long bones with slender diaphyses, flared metaphyses, and overgrown epiphyses are developed later *(3)*.

Our patient presents a typical physical appearance and characteristic exploratory findings of progeria. Furthermore, the alterations observed in the blood tests (hyperphosphatemia, elevated platelet counts, and prolongation of prothrombin time) have been reported as progeria features in a recent publication by Merideth et al *(5)*. The mechanism of elevated serum phosphorus levels associated with inappropriately low fractional excretion of phosphorus is unknown, but data indicate that the set point for renal phosphorus reabsorption may be slightly altered *(6)*. It has been hypothesized that impaired renal expression of klotho and fibroblast growth factor 23 could be implicated *(7)*.

At the moment, there are no therapeutic options for human PSs with the exception of treating complications of the disease. Secondary fractures due to severe osteoporosis, as it is in our patient's situation, dramatically worsen the quality of life of patients with progeria. Therefore, aggressive treatment of bone disease must be warranted.

Pharmacologic therapies for osteoporosis include bisphosphonates as first-line therapy. A recent study in a mouse model of human premature aging showed that combined treatment with statins (pravastatin) and aminobisphosphonates