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Case Report

Losartan as a Steroid-Sparing Adjunct in a Patient With Features of Refractory Camurati-Engelmann Disease

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ABSTRACT

Objective: The treatment of Camurati-Engelmann disease (CED) involves the use of glucocorticoids, analgesics, and bisphosphonates; experience with the use of losartan is limited. Our objective was to describe the case of a patient diagnosed with CED whose symptoms remained refractory while on steroids and bisphosphonates and who was successfully treated with losartan.

Case Report: A 27-year-old woman presented with bone pain involving her extremities and large joints for 1 year. Clinical examination revealed bone tenderness and proximal myopathy with elevated C-terminal peptide of type 1 collagen (1617 pg/mL; normal range, 137-573 pg/mL) and N-terminal propeptide of type 1 procollagen levels (163 ng/mL; normal range, 5.1-58.3 ng/mL). Calcium (9.4 mg/dL; normal range, 8.3-10.4 mg/dL), phosphate (3.4 mg/dL; normal range, 2.5-4.5 mg/dL), and parathyroid hormone (62 pg/mL; normal range, 8-80 pg/mL) levels were within the normal range. Radiographs showed hyperostosis involving the diaphyseal region of long bones of the lower and upper limbs, and a provisional diagnosis of CED was made. She was treated with prednisolone, 30 mg daily, with which she reported some improvement. As exogenous Cushing syndrome had developed in her because of prednisolone, its dose was tapered. Subsequently, her bone pain worsened. Thereafter, she was initiated on oral alendronate. Due to persistent pain, losartan was added, after which she had marked decrease in bone pain with a reduction in the C-terminal peptide of type 1 collagen (375 pg/mL) and N-terminal propeptide of type 1 procollagen (50 ng/mL) levels.

Discussion: Occasionally, CED presents therapeutic challenges, and when its symptoms remain refractory to conventional doses of steroids and bisphosphonates, other options may be needed. The above-mentioned patient was initiated on losartan, which acts by downregulation of transforming growth factor β1, leading to the reduction in pain.

Conclusion: Losartan downregulates transforming growth factor β1 and may be offered as a steroid-sparing option in individuals diagnosed with CED if symptoms remain refractory to conventional treatment.

Introduction

Camurati-Engelmann disease (CED), also known as progressive diaphyseal dysplasia, is a rare autosomal dominant form of skeletal dysplasia characterized by bone pain, waddling gait, easy fatigability, and muscle weakness resulting from progressive sclerosis of long bones and the skull.[1] It is caused by a missense gain-of-function alteration of transforming growth factor (TGF) β1.[2] We report the case of a young woman provisionally diagnosed with CED in the third decade of life and the treatment challenges associated with the disease. As the patient's symptoms of bone pain had persisted despite being on steroids and bisphosphonates, losartan, an angiotensin receptor blocker that also downregulates TGFβ1 signaling, was added as a steroid-sparing agent, and this resulted in a dramatic improvement in her symptoms.

See related Commentary by Kelley and Davidge-Pitts in this issue (https://doi.org/10.1016/j.aace.2021.08.001).

Abbreviations: CED, Camurati-Engelmann disease; TGF, transforming growth factor.

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Case Report

A 27-year-old woman presented to the endocrinology outpatient department with insidious onset of progressive pain in both her legs and arms for the last 1 year. She also had pain in all her large joints and difficulty in getting up from a squat. There was no history of fractures or renal stones. She was the second born of a nonconsanguineous marriage. She was home delivered without any perinatal complications. Her developmental milestones were normal. Her mother had postpolio residual paralysis; however, her family history was otherwise unremarkable. She attained menarche at 16 years and currently had regular menstrual cycles.

On clinical examination, she had a height of 144 cm (midparental height, 145 cm). Her body weight was 45.5 kg, and her body mass index was 21.9 kg/m^2. There was tenderness in both thighs with no associated swelling. She had evidence of a waddling gait. There was no facial dysmorphism. Her sclera and dentition were normal. Visual and hearing assessments were normal. There was no evidence of macrocephaly or cranial nerve involvement. Active and passive joint movements were normal. Bone biochemical investigations revealed high alkaline phosphatase levels, with elevated levels of bone turnover markers (Table). Serum electrolytes and creatinine levels were normal. Arterial blood gas estimation had ruled out metabolic acidosis. Radiographs revealed cortical thickening involving the diaphyseal region of both femurs (Fig. 1) and long bones of the upper limbs (Fig. 2). A technetium-99m methylene diphosphonate bone scan (Fig. 3) was performed, which showed increased tracer uptake in the diaphysis of long bones (bilateral humerus, ulna, radius, femur, tibia, and fibula).

With the abovementioned presentation and radiographic evidence of predominant diaphyseal hyperostosis, a diagnosis of CED was made. She was started on a weight-based dose (0.5 mg/kg) of oral prednisolone at a dosage of 30 mg, which she continued for 6 months. Subsequently, exogenous steroid-induced Cushing syndrome with weight gain, pedal edema, proximal myopathy, and striae over the arms and abdomen developed in her. Thereafter, prednisolone was gradually tapered. Following the steroid dose tapering, there was a worsening of symptoms, with the patient experiencing excruciating pain in her thighs. She was initiated on oral alendronate 70 mg weekly, in addition to steroids. Due to persistent pain in her bones, she was also started on losartan at a dosage of 25 mg once daily, which was continued further for 6 months. Calcium and cholecalciferol supplementations were given to ensure a calcium- and vitamin D–replete status. Following the initiation of losartan, there was a marked reduction in her pain, with eventual normalization of bone turnover marker levels and a significant decrease in the levels of alkaline phosphatase. She continues to be on a regular outpatient follow-up.

Table
Bone Biochemistry at the Presentation and 6-Month Follow-Up

Bone biochemistry	Normal range	At presentation	At the 6-mo follow-up
Corrected calcium, mg/dL	8.3-10.4	9.4	9.6
Phosphate, mg/dL	2.5-4.5	3.4	3.8
Creatinine, mg/dL	0.5-1.2	0.5	0.4
25-hydroxy vitamin D, ng/mL	30-75	25.5	…
PTH, pg/mL	8-80	62	…
P1NP, ng/mL	15.1-58.3	163	50
CTX, pg/mL	137-573	1617	375
Alkaline phosphatase, U/L	40-125	300	195

Abbreviations: CTX = C-terminal peptide of type 1 collagen; P1NP = N-terminal propeptide of type 1 procollagen; PTH = parathyroid hormone.

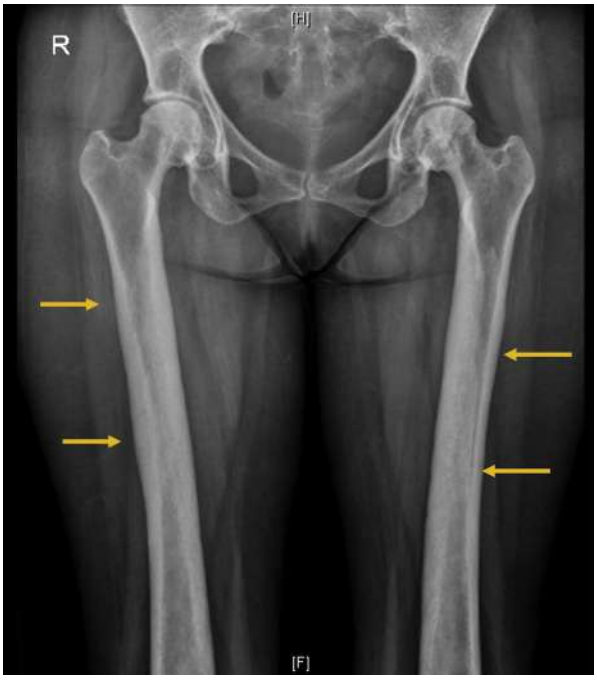

Fig. 1. Diaphyseal hyperostosis (arrows) involving the right and left femur. *R* = right.

Discussion

In this case report, we describe a young woman diagnosed with CED in the third decade of life and the treatment challenges associated with the disease. As the patient's symptoms of bone pain persisted despite being on steroids and bisphosphonates, losartan, an angiotensin receptor blocker that also downregulates TGFβ1 signaling, was added as a steroid-sparing agent, and this resulted in a dramatic improvement in her symptoms with a reduction in the levels of the biochemical markers of bone turnover.

CED is a rare disease that was first described by Cockayne[3] in 1920. Its hereditary nature was described by Camurati, after which Engelmann reported a single case with muscle weakness and bone involvement. Currently, approximately 300 patients have been identified in the world literature.[4] The increased TGFβ1 activity stimulates osteoblasts and inhibits osteoclasts that affects remodeling and leads to hyperostosis and thickening of the diaphysis of long bones with epiphyseal sparing.[5] TGFβ1 also suppresses myoblast maturation and adipogenesis.[6,7] The average age of onset is the second decade; however, it has been reported at birth and up to 76 years of age.[8]

Individuals with CED present with severe bone pain; proximal muscle weakness; poor muscular development; a wide-based, waddling gait; easy fatigability; and headaches.[8] The bone pain is constant, aching, and most intense in the lower limbs, increasing with activity, stress, and cold weather.[1] Osteosclerosis of the skull can lead to macrocephaly, frontal bossing, enlargement of the mandible, proptosis, cranial nerve impingement, increased intracranial pressure, and headaches. Rare manifestations include anemia, anorexia, hepatosplenomegaly, decreased subcutaneous tissue, atrophic skin, delayed dentition, extensive caries, delayed puberty, and hypogonadism.[9]

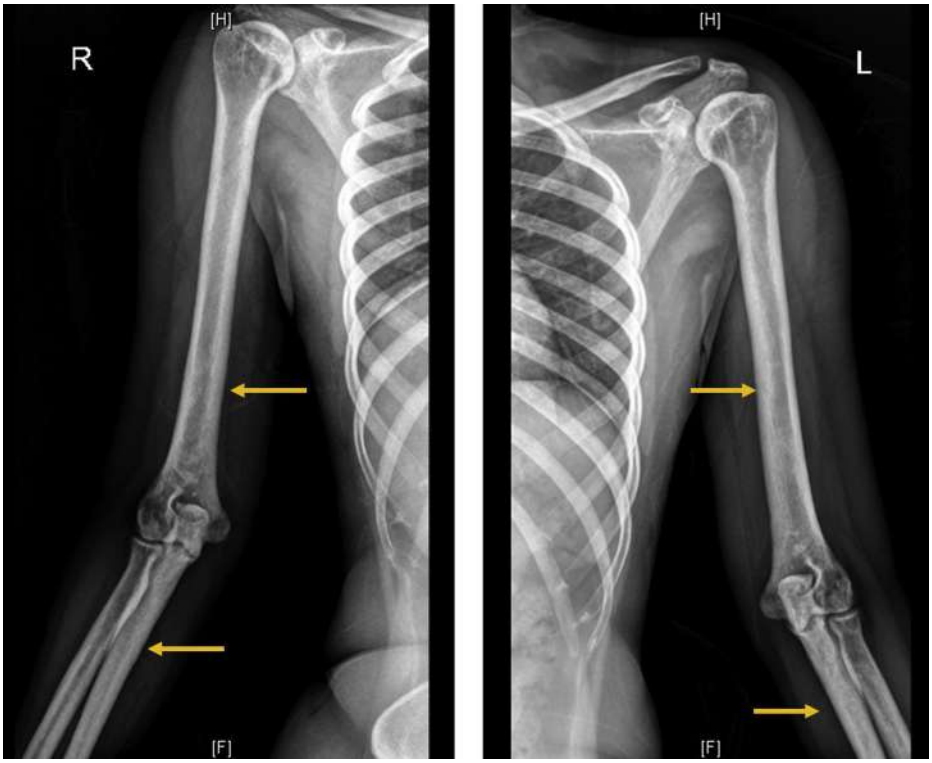

Fig. 2. Diaphyseal hyperostosis (arrows) involving long bones of the upper limbs. *L* = left; *R* = right.

CED initially begins in the diaphyses and extends to the metaphyses, sparing the epiphyses. Radiologic features include periosteal involvement with uneven cortical thickening, increased diameter, and endosteal bone sclerosis.[10] The bones that are usually affected are the femur, tibia, fibula, humerus, ulna, and radius. It may also involve the mandible, scapulae, clavicles, pelvis, and skull base.[10]

The diagnosis of the disease is based on the clinical symptoms and laboratory findings but is confirmed by the radiologic images. Although elevated alkaline phosphatase levels do not necessarily define CED, in literature, many authors have reported that an increased alkaline phosphatase level is encountered in many patients. CED is pathophysiologically characterized by continued TGFβ signaling. TGFβ has multiple effects on bone cells. Osteoblasts are directly affected by TGFβ, which can induce their differentiation or proliferation. TGFβ inhibits the formation of osteoclast precursors and bone resorption and, at greater concentrations, has inhibitory effects on isolated osteoclasts, the cells responsible for bone resorption. TGFβ may act as a bone-coupling factor linking bone resorption to bone formation. Thus, alkaline phosphatase levels may be marginally elevated in this condition with a probable uncoupling of bone formation and resorption.[11,12]

Although there are no standard guidelines for the therapy of CED, the use of nonsteroidal anti-inflammatory drugs, acetaminophen, bisphosphonates, glucocorticoids, calcitonin, and losartan has been described. Surgery is generally done for cranial nerve decompression and to relieve intracranial pressure in cases with skull hyperostosis.

Glucocorticoids are the cornerstone in the treatment of CED because they increase the apoptosis of the osteoblasts and osteocytes and also allow the proliferation and differentiation of the osteoclasts.[8] They reduce pain and also inhibit TGFβ1-stimulated muscle fibrosis. Prednisolone at a dosage of 0.5 to 1 mg/kg/d, followed by a rapid reduction in the dose to avoid side effects, is used to control the bone pain and fatigue. Prednisolone has typically been used in many cases; however, its untoward side effects (growth impairment in children, worsening osteopenia, and weight gain) may limit its duration of therapy. Losartan, an angiotensin II receptor blocker, downregulates the signaling of TGFβ1, resolves pain, and improves bone mineral density and fat mass accrual; it has demonstrated improvement in the symptoms associated with CED.[13]

As of now, there are no consensus guidelines on the treatment of CED. As such, the treatment of CED remains empiric. Therefore, the authors believe that the initiation of the treatment may be stepwise. As there are conflicting reports on the use of losartan, the authors, at their center, initiate treatment with glucocorticoids and assess the patient periodically with the addition of bisphosphonates and/or losartan depending on the patient's improvement and symptomatology. In literature, some case reports have demonstrated significant benefits with the initiation of losartan, improving the patient's symptomatology and the overall well-being and quality of life.[13-15]

In the abovementioned case, the patient had some improvement in symptoms after she was started on steroids; however, within a year, there was a flareup of the bone pain once the dose of steroids was tapered. The pain was severe enough for her to take multiple doses of opioid analgesics in a week. Exogenous Cushing syndrome had also developed in her due to steroids. The addition of losartan resulted in a significant reduction in pain and a decrease in the levels of bone turnover markers of our patient with an improvement in muscle mass and function. The patient is being continued on alendronate, losartan, and prednisolone along with calcium and cholecalciferol supplementations.

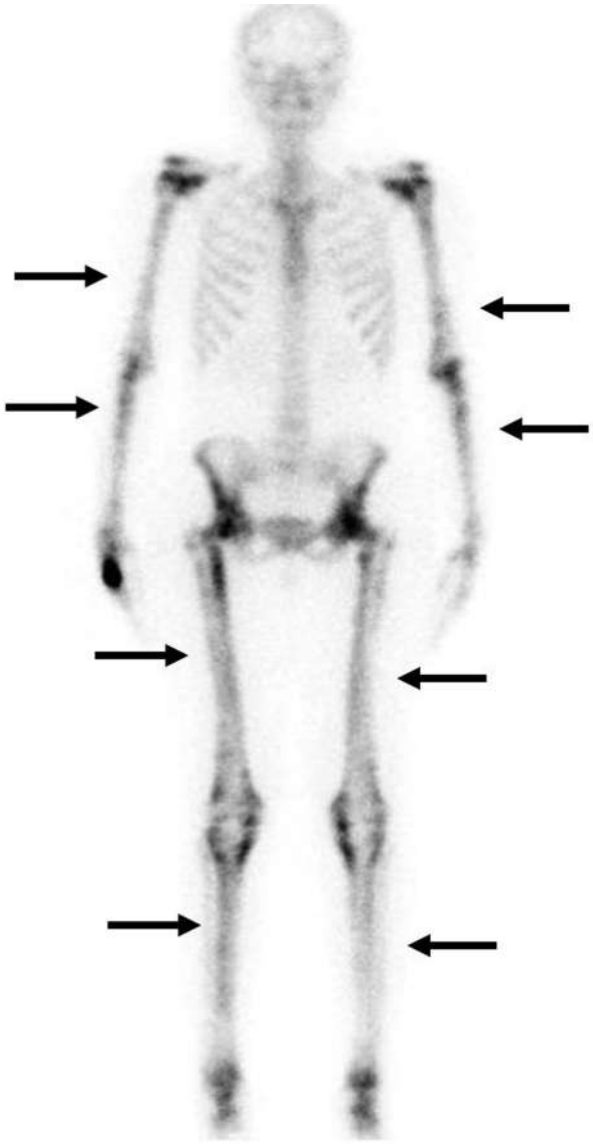

Fig. 3. Technetium-99m methylene diphosphonate scan showing increased tracer uptake (arrows) in the involved bones.

Conclusion

In summary, CED presents with a wide range of clinical manifestations, including muscle weakness and motor disturbance in early childhood and limb pain in later childhood or adulthood, and, occasionally, it may be asymptomatic. Awareness of this rare disease entity may be important for a timely, accurate diagnosis. Besides oral steroids and bisphosphonates, losartan, which downregulates TGFβ1 signaling, may be offered as a viable and steroid-sparing therapeutic option, especially in refractory cases.

Disclosure

The authors have no multiplicity of interest to disclose.

Ethical Disclosure

Informed consent was taken from the patient. The authors declare that no patient data appear in the article.

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